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## SULFATHIAZOLE AND SULFAPYRIDINE

### IN THE TREATMENT OF PNEUMONIA IN INFANCY AND CHILDHOOD


STEWART C. WAGONER, M.D.
AND
WILLIAM F. HUNTING, M.D.
CINCINNATI


Sulfathiazole [2 (para-amino-benzene-sulfonamido) thiazole], the thiazole derivative of sulfanilamide, has been offered to the medical profession for clinical trial. Experimental work, both in vitro and in vivo, by Barlow and Homburger,[1] McKee, Rake, Greep and van Dyke,[2] Long and Bliss,[3] and others has indicated that it probably is as effective in the treatment of pneumonia and certain other infections as sulfapyridine. Studies on the toxicity of the drug in animals by Long, Haviland and Edwards [4] and van Dyke, Greep, Rake and McKee [5] indicated that the drug could probably be safely used clinically under carefully controlled conditions. During the past two years numerous articles have appeared which would seem to indicate that sulfapyridine is an effective agent in the treatment of pneumonia. Among these publications was that of Wilson, Spreen, Cooper, Stevenson, Cullen and Mitchell [6] at the Children's Hospital and in the pediatric wards of the Cincinnati General Hospital, in which there was a study of a group of patients receiving sulfapyridine and a control group not receiving this drug. The present report is a study of the relative effectiveness of sulfapyridine and sulfathiazole in the treatment of pneumonia in infancy and childhood.

The patients were allocated to one of two groups on admission, designated respectively as "sulfapyridine" and "sulfathiazole," in such a manner that after completion of the study the two groups would be comparable, at the time therapy was instituted, in regard to age and duration and severity of the pneumonia. No attempts were made to differentiate between croupous pneumonia and bronchopneumonia. Because of possible differences of assimilation of sulfapyridine and sulfathiazole, it was decided to make the comparison between their effects on the basis of the levels of the free drug in the blood. From the work done last year by Wilson and his co-workers it was felt that a level of free sulfapyridine in the blood of from 4 to 6 mg. per hundred cubic centimeters was therapeutically adequate, and it was accordingly decided to attempt to administer sulfapyridine and sulfathiazole in this study in doses which would keep the blood concentration between these levels. The majority of patients were started on 1 grain (0.06 Gm.) of sulfapyridine per pound (0.5 Kg.) of body weight and 1½ to 2 grains (0.1 to 0.13 Gm.) of sulfathiazole per pound (0.5 Kg.) of body weight. Daily blood levels were ascertained, and the dose was altered accordingly so that the blood levels would be properly maintained.

On admission the material for pharyngeal cultures for pneumococci, cultures of the blood, roentgenograms of the chest and complete blood cell counts were obtained on all patients, and other studies and cultures were done as indicated. Chemotherapy was instituted immediately, half the calculated dose for twenty-four hours being given as an initial amount, and thereafter the drug was administered every four hours as long as indicated, except in a few instances when it was given every three hours or every eight hours.

All patients were studied closely in both groups, my colleague and I keeping in mind the final analyses to be made and the observations to be recorded. Those patients who had empyema on admission were excluded from the series, but those who had sterile pleural effusions were included in the final group. Four patients were discarded from the final analysis since in their cases the diagnoses were subsequently proved to be tuberculous pneumonia. None of these patients showed any response to chemotherapy. It was decided not to evaluate the day of clinical improvement since it was much less of an objective determination than the day of significant fall in temperature, although both fall in temperature and apparent clinical improvement occurred on the same day except in a few instances.

Most clinicians have agreed that a fall in temperature should occur within forty-eight hours if it is to be attributed to chemotherapy. In this study all patients whose temperatures were not below 100 F. (37.5 C.) in forty-eight hours and then remained below this level were designated as having an unsatisfactory response. All patients received the drug continuously until the temperature had remained below 100 F. rectally for seventy-two hours.

During the course of the study, daily physical examinations were made and special graphic records were kept of all physical and noteworthy changes. Daily estimations were made of the blood level of the drug on 0.2 cc. of capillary blood by using a photoelectric colorimeter and a modification of the method of Marshall

---


E. R. Squibb & Sons furnished the sulfathiazole used in this study.



From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.



Advice regarding the statistical methods employed was given by Estelle W. Brown, statistician of the Children's Hospital Research Foundation.


1. Barlow, O. W., and Homburger, E.: Proc. Soc. Exper. Biol. & Med. **42**: 792 (Dec.) 1939.
2. McKee, Clara M.; Rake, Geoffrey; Greep, R. O., and van Dyke, H. B.: Proc. Soc. Exper. Biol. & Med. **42**: 417 (Nov.) 1939.
3. Long, P. H., and Bliss, Eleanor A.: Proc. Soc. Exper. Biol. & Med. **43**: 324 (Feb.) 1940.
4. Long, P. H.; Haviland, J. W., and Edwards, L. B.: Proc. Soc. Exper. Biol. & Med. **43**: 328 (Feb.) 1940.
5. van Dyke, H. B.; Greep, R. O.; Rake, Geoffrey, and McKee, Clara M.: Proc. Soc. Exper. Biol. & Med. **42**: 410 (Nov.) 1939.
6. Wilson, A. T.; Spreen, A. H.; Cooper, M. L.; Stevenson, F. E.; Cullen, G. E., and Mitchell, A. G.: Sulfapyridine in Treatment of Pneumonia in Infancy and Childhood, J. A. M. A. **112**: 1435 (April 15) 1939.

and Litchfield.[7] Following the blood count on admission, hemoglobin determinations and leukocyte counts were made every three days unless they were indicated more frequently, and daily urinalyses were done in most cases.

### ANALYSIS OF MATERIAL

One hundred and nine patients with pneumonia were treated and the results analyzed in the manner outlined.

TABLE 1.—*Analysis of 109 Cases of Pneumonia*

| | Sulfathiazole Group (Total 55) | Sulfapyridine Group (Total 54) |
|---|---|---|
| Age | | |
| Birth to 11 months | 7 | 4 |
| 12 to 23 months | 18 | 17 |
| 2 to 4 years | 14 | 19 |
| 5 years and over | 16 | 14 |
| Severity | | |
| Mild | 3 | 5 |
| Moderate | 30 | 32 |
| Severe | 21 | 16 |
| Very severe | 1 | 1 |
| Estimated duration of pneumonia when therapy was started | | |
| 1 day | 4 | 6 |
| 2 days | 22 | 21 |
| 3 days | 17 | 17 |
| 4 days | 10 | 7 |
| 5 days | 1 | 2 |
| 6 days | 1 | 1 |
| Average | 2.7 | 2.6 |
| Type of pneumonia | | |
| Croupous | 13 | 12 |
| Bronchopneumonia | 42 | 42 |

Of these patients 55 received sulfathiazole and 54 received sulfapyridine. Table 1 demonstrates the comparison between the two groups, related to age and to the severity and duration of pneumonia, when the treatments were started. While no attempt was made to differentiate between croupous pneumonia and bronchopneumonia in grouping the cases, table 1 also shows how closely these two types were distributed by chance alone

As previously stated, the "sulfapyridine group" was started on 1 grain per pound of body weight per twenty-four hours, the initial dose being one half of the calculated twenty-four hour dose. The "sulfathiazole group" received from 1½ to 2 grains per pound of body weight per twenty-four hours and, similarly, one half of the

TABLE 2.—*Analysis of Determinations of Drugs in the Blood*

| | Mean | Standard Deviation |
|---|---|---|
| Free, mg. per 100 cubic centimeters | | |
| Sulfathiazole | 5.3 | 1.8 |
| Sulfapyridine | 6.3 | 2.5 |
| Conjugate, mg. per 100 cubic centimeters | | |
| Sulfathiazole | 1.1 | 0.46 |
| Sulfapyridine | 1.6 | 1.00 |
| Total, mg. per 100 cubic centimeters | | |
| Sulfathiazole | 6.4 | 2.0 |
| Sulfapyridine | 7.9 | 2.7 |
| | | Average Number of Days of Therapy |
| Sulfathiazole | | 4.7 days |
| Sulfapyridine | | 4.6 days |

calculated twenty-four hour dose initially. Considerable difficulty was encountered in attempting to regulate the level of the free drug in the blood to between 4 and 6 mg. per hundred cubic centimeters, and it was often necessary to change the dose daily. Table 2 shows that the average number of days of treatment in both groups was essentially the same, namely, four and seven-tenths days with sulfathiazole and four and six-tenths days with sulfapyridine.

7. Marshall, E. K., Jr., and Litchfield, J. T., Jr.: Science **88**: 85 (July 22) 1938.

The daily blood levels of the drugs were analyzed in both series, and the results are given in table 2. The mean level of free sulfapyridine was slightly higher, i. e. 6.3 mg. per hundred cubic centimeters, but showed a standard deviation of 2.5 as compared with sulfathiazole, of which a mean level of 5.3 mg. per hundred cubic centimeters was found, and the standard deviation was 1.8. If they are analyzed statistically there is a significant difference between the two free levels, and the probability (P) is 0.02 that this difference is due to chance alone.

Table 3 shows the organisms observed in the cultures of material from the pharynx. No intensive bacteriologic study was made in this series other than the routine cultures on admission, and the number of pathogenic organisms found is less than that reported by other workers by whom more emphasis was placed on this factor. The number of cases is too few to warrant an analysis of the type of organism in relation to severity, type of pneumonia or effect of therapy.

Of the 109 patients only 2 were found to have bacteremia on admission, both being in the sulfathiazole

TABLE 3.—*Types of Organisms Isolated from Throats* *

| Type of Organism | Sulfathiazole Group | Sulfapyridine Group |
|---|---|---|
| Pneumococcus type: | | |
| I | 3 | 4 |
| II | 2 | 0 |
| III | 0 | 1 |
| IV | 0 | 3 |
| V | 4 | 0 |
| VI | 6 | 3 |
| VII | 1 | 0 |
| IX | 1 | 1 |
| XI | 1 | 2 |
| XIV | 1 | 3 |
| XV | 1 | 1 |
| XVI | 1 | 1 |
| XVIII | 1 | 0 |
| XIX | 2 | 3 |
| XXIII | 1 | 4 |
| XXV | 0 | 1 |
| XXVIII | 1 | 0 |
| XXIX | 1 | 0 |
| XXXIII | 1 | 0 |
| Hemolytic streptococcus | 5 | 4 |
| Hemolytic Staphylococcus aureus | 6 | 4 |
| Nonpathogenic or negative culture | 16 | 27 |

* This includes all pneumococci observed, whether alone or in combination with other types.

group and in the younger age group. The causative organisms in these patients were type II and type XXXIII pneumococci respectively. Both patients subsequently recovered.

There were two deaths during the course of this study. One death was of an infant aged 15 months who was moribund on admission and who had bilateral bronchopneumonia and active rickets. The throat culture yielded type XXXIII pneumococcus. The serum calcium level was 3.8 mg. per hundred cubic centimeters, and the phosphorus level was 9.1 mg. on admission, although there was no clinical evidence of tetany. The patient received two doses of sulfathiazole but died thirteen hours later. Permission for necropsy was refused. This patient was excluded from the final analysis of the series. The other patient was an infant aged 13 months with extensive bilateral bronchopneumonia. The throat culture yielded type I pneumococcus. There was an initial response to the drug with a fall in temperature, but the infant died suddenly twenty-seven hours after admission. At necropsy an extensive bilateral bronchopneumonia and a dilated right ventricle and auricle were the only positive manifestations. This patient was included in the study.

### ANALYSIS OF THE RESULTS

1. *Course of the Pneumonia.*—Table 4 demonstrates the average day for both sulfathiazole and sulfapyridine groups on which there was a significant fall in temperature and also the day of clinical recovery in relation to the day of the onset of pneumonia and the day of beginning of treatment. The two drugs appeared to be equally effective, and the difference in days between the two groups is not statistically significant in any of the analyses. In both groups, the significant fall in temperature was approximately thirty-six hours after treatment was started, and clinical recovery occurred on the average of five and one-half days following the beginning of drug administration in the sulfathiazole group and six and two-tenths days in the sulfapyridine group. The temperature of 55 patients treated with sulfathiazole fell within twenty-four hours to below 100 F. (37.5 C.) rectally and remained below this level in 44 cases, whereas, excluding the 1 patient who died, this fall in temperature occurred within twenty-four hours in only 32 of the 53 patients in the sulfapyridine group. This difference between the two groups is not statistically significant and in a series of this size could well be due to chance alone. It may be mentioned, however, that clinical observation suggested that there was a better response to sulfathiazole than to sulfapyridine.

TABLE 4.—*Clinical Results in 109 Cases of Pneumonia*

| | Sulfathiazole Group | Sulfapyridine Group | Difference in Days |
|---|---|---|---|
| Mean day of pneumonia at | | | |
| Significant fall in temperature | 3.90 | 4.30 | 0.40 |
| Clinical recovery | 9.2 | 8.9 | 0.3 |
| Mean day of treatment at | | | |
| Significant fall in temperature | 1.5 | 1.4 | 0.1 |
| Clinical recovery | 5.5 | 6.2 | 0.7 |

2. *Drug Response Unsatisfactory: Failures and Relapses.*—Of the group of 55 patients treated with sulfathiazole 2 apparently showed an unsatisfactory response to this therapy, since their temperatures failed to fall below 100 F. (37.5 C.) rectally within forty-eight hours. Of the 53 patients in the sulfapyridine group there were 8 who failed to show the drop in temperature within forty-eight hours. This apparent difference in favor of sulfathiazole was analyzed statistically and chi square was found to be 2.96 and P to be between 0.10 and 0.05. Therefore it must be stated that in a series of this size there probably is no significant difference between the number of unsatisfactory responses in the two groups. One of the patients in the sulfathiazole group and 2 in the sulfapyridine group had relapses. All 3 of these patients had shown an initial satisfactory response but manifested a rise in temperature and a return of symptoms when chemotherapy was discontinued. One patient in the sulfathiazole group failed to respond and, although receiving the drug continuously, did not become afebrile until after fifteen days of such treatment.

Three patients who were originally included in the study were excluded in the final analysis. Two of these patients received sulfapyridine for three days but manifested a progression of symptoms. A change was made to sulfathiazole therapy and the temperature promptly fell to normal within twenty-four hours and marked clinical improvement was evident. Cultures taken on material from the throat yielded hemolytic Staphylococcus aureus and pneumococcus type XVII. The other patient received sulfathiazole for three and one-half days with no effect. Sulfapyridine therapy was then started and the temperature fell to normal in thirty-six hours with resultant clinical improvement. Type IV pneumococcus was found on cultures of material taken from the throat. These significant falls in temperature may have been only coincidental crises in the normal course of pneumonia but they suggest the advisability of changing drugs when the response is unsatisfactory to one or the other of them.

TABLE 5.—*Complications in 109 Cases of Pneumonia*

| | Sulfathiazole Group | | Sulfapyridine Group | |
|---|---|---|---|---|
| | On Admission | After Admission | On Admission | After Admission |
| Empyema | 0 | 0 | 0 | 1 |
| Bacteremia | 2 | 0 | 0 | 0 |
| Otitis media acute, suppurative | 6 | 0 | 4 | 3 |
| Otitis media acute, nonsuppurative | 8 | 1 | 6 | 5 |
| Pleural effusion | 1 | 0 | 2 | 0 |
| Congenital heart disease | 0 | .. | 1 | .. |
| Rheumatic heart disease | 2 | 0 | 1 | 0 |

### INCIDENCE OF COMPLICATIONS

Table 5 is an analysis of complications in the two groups of patients. The series is too small to permit one to evaluate any difference in these findings, although there is an apparent difference between the two groups in the incidence of nonsuppurative otitis media which occurred after admission. Of the 55 patients in the sulfathiazole group there was 1 who had acute nonsuppurative otitis media, and in the 54 patients in the sulfapyridine group there were 5 who had this complication. Empyema developed in one patient in the sulfapyridine group.

### TOXIC EFFECTS OF SULFAPYRIDINE AND SULFATHIAZOLE

In 1 patient cyanosis developed after the administration of sulfathiazole, but after the administration of sulfapyridine it developed in 3 patients. None of these patients manifested cyanosis on admission and it occurred subsequent to initial clinical improvement, thus suggesting that it was due to the drug.

Ten patients in the sulfathiazole group and 5 patients in the sulfapyridine group had cyanosis on admission which disappeared with clinical improvement and a significant fall in temperature, thus suggesting that it was due to the pneumonia.

TABLE 6.—*Toxicity of Drug as Shown by Incidence of Vomiting*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Number of patients who vomited | | | | | | | |
| Sulfathiazole group | 18 | | | | | | |
| Sulfapyridine group | 34 | | | | | | |
| Number of times | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Sulfathiazole group | 10 | 3 | 3 | 1 | 1 | | |
| Sulfapyridine group | 9 | 13 | 5 | 2 | 3 | 1 | 1 |
| Median for sulfathiazole group | 1.9 | | | | | | |
| Median for sulfapyridine group | 2.5 | | | | | | |

Microscopic hematuria appeared in only 1 patient in the sulfathiazole group and in no patient in the sulfapyridine group.

No instances of hemolytic anemia were discovered. Leukopenia was noted in 2 patients, 1 in each group. A leukocyte count of 4,900 was found in 1 patient on the fifth day of treatment with sulfathiazole and a leukocyte count of 3,600 in 1 patient on the third day of treatment

with sulfapyridine. Therapy was discontinued immediately when the leukopenia was discovered, and the leukocyte count promptly returned to normal levels.

No morbilliform rash or other type of rash occurred which could be attributed to drug therapy.

Vomiting was the chief toxic manifestation noted. It was observed in 18 patients treated with sulfathiazole and in 34 treated with sulfapyridine. Table 6 indicates the incidence of this symptom and shows that in those who vomited it occurred on the average one and nine-tenths times in the sulfathiazole group and two and five-tenths times in the sulfapyridine group. How much of the vomiting was due to the pneumonia and how much due to the administration of the drug cannot be determined.

### SUMMARY AND CONCLUSIONS

1. A control study of pneumonia in infancy and childhood was made on two comparable groups, one receiving sulfathiazole and the other sulfapyridine. No control group of nonspecifically treated patients was included since the efficacy of chemotherapy in pneumonia in general is well established. Careful selection was made to assure comparable groups in relation to the factors of age and duration and severity of pneumonia and the time at which the drug therapy was started. For comparison an attempt was made to adjust the levels of the free drug in both groups to between 4 and 6 mg. per hundred cubic centimeters.

2. One hundred and nine patients with pneumonia were observed in this study, 55 of whom received sulfathiazole and 54 sulfapyridine. An analysis of the characteristics of the disease on admission and of the levels of the free drug in the blood achieved demonstrated that the two groups were suitable for comparison.

3. No significant statistical difference was demonstrated between sulfathiazole and sulfapyridine in relation to the time at which a significant fall of temperature occurred or the time at which there was clinical recovery. In the sulfathiazole group the mean time after treatment at which the temperature fell to below 100 F. (37.5 C.) and remained below this level was one and five-tenths days; in the sulfapyridine group it was one and four-tenths. In the sulfathiazole group the mean time at which there was apparent clinical recovery was five and five-tenths days; in the sulfapyridine group it was six and two-tenths.

4. Unsatisfactory response to the drug occurred in 2 patients in the sulfathiazole group and in 8 patients in the sulfapyridine group. This is probably not a statistically significant difference. There was one relapse in the sulfathiazole group and there were two relapses in the sulfapyridine group. One patient treated with sulfathiazole followed a course apparently uninfluenced by the drug.

5. It is suggested that a change might be made from one drug to the other in those instances in which a significant fall in temperature fails to occur within forty-eight hours after therapy is started, or that serum therapy might then be employed.

6. There was one death of a patient treated with sulfapyridine. Empyema subsequently developed in another patient after an initial good response to sulfapyridine.

7. Vomiting occurred in 18 patients treated with sulfathiazole and in 34 patients treated with sulfapyridine, but an evaluation of the incidence of this symptom as a toxic effect of the drugs is confused by the fact that pneumonia itself is a cause of vomiting. Hematuria developed in 1 patient while taking sulfathiazole. Leukopenia occurred in 1 patient taking sulfathiazole and in 1 patient taking sulfapyridine.

8. This study indicates that sulfathiazole is as effective as sulfapyridine in the treatment of pneumonia. No marked toxicity was noted from the administration of sulfathiazole or of sulfapyridine when it was administered over an average period of five days.

Elland Avenue and Bethesda.

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## SULFAPYRIDINE THERAPY IN LOBAR PNEUMONIA ASSOCIATED WITH LEUKOPENIA

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When lobar pneumonia is associated with leukopenia instead of the usual leukocytosis, a therapeutic problem is presented as to the propriety of administering sulfapyridine. On the one hand it is known that sulfapyridine itself is capable of producing serious or even fatal leukopenia and neutropenia. Thus there would seem to be a justifiable hesitation in using this drug, lest it further depress the low leukocyte count to a dangerous degree. On the other hand, sulfapyridine is probably the most valuable single agent in the treatment of lobar pneumonia. Its use appears particularly indicated in cases of lobar pneumonia with leukopenia because these cases usually represent severe infections and present the worst prognosis. Middleton and Gibbon [1] noted that all their patients with leukopenia of less than 5,000 leukocytes per cubic millimeter died. Even those patients with relative leukopenia (5,000 to 10,000 leukocytes per cubic millimeter) had a much higher mortality rate than those with leukocytosis. The most extreme example of leukopenia associated with lobar pneumonia was a fatal case, reported by Menninger,[2] in which the leukocyte count was as low as 150 per cubic millimeter.

The danger of sulfapyridine leukopenia or neutropenia is relatively slight. Large series of patients with lobar pneumonia have been treated with sulfapyridine without the occurrence of this hematologic complication. There is no evidence in the reported cases that sulfapyridine leukopenia appeared more readily when the initial leukocyte count was low than when it was considerably elevated. Furthermore, in almost all cases leukopenia and neutropenia appeared only after the drug had been administered for two weeks or longer and in a total dose of 50 Gm. or more. This is a longer period of administration and a larger quantity than is ordinarily required in the treatment of lobar pneumonia. Finally it should be emphasized that leukopenia in cases of lobar pneumonia is the result of the infection itself and that any measure, such as the administration of sulfapyridine, which tends to overcome the infection should benefit the leukopenia by removing the causative factor.

In the following two cases of severe lobar pneumonia associated with striking leukopenia, sulfapyridine therapy was followed by a rise in the patient's leukocyte

From the Medical Service of Dr. George Baehr, the Mount Sinai Hospital.

1. Middleton, Richard, and Gibbon, J. H., Jr.: The Prognostic Value of the Initial Leukocyte and Differential Count in Lobar Pneumonia, Am. J. M. Sc. **180**: 31 (July) 1930.

2. Menninger, W. C.: Extreme Leukopenia in Lobar Pneumonia, J. A. M. A. **85**: 435 (Aug. 8) 1925.

count and clinical improvement after the usual forms of therapy, including massive doses of specific antipneumococcus serum, had been ineffective.

### REPORT OF CASES

CASE 1.—A Negro laborer aged 40 was admitted to the hospital on April 24, 1940. There was a history of persistent alcoholism and vagrancy. For two months prior to admission he had been consuming about a quart of corn whisky daily. Ten days before admission he had been suffering from an infection of the upper part of the respiratory tract.

The present illness began acutely three days before admission with severe cough, the expectoration of bloody sputum and pain in the chest. Intense headache, fever and malaise soon followed. The patient was hospitalized because of continued fever, cough and prostration.

On admission the patient appeared acutely ill. His temperature was 103.6 F., respiratory rate 44 and pulse rate 120. There was herpes of the lips. The pharyngeal mucosa was congested. There were signs of consolidation over the middle and lower lobes of the right lung. The remainder of the examination was negative. The diagnosis was lobar pneumonia of the lower and middle lobes of the right lung.

About half an hour after an initial dose (3 Gm.) of sulfathiazole had been administered a blood count revealed 1,400 white blood cells per cubic millimeter, with 7 per cent neutrophils, 14 per cent lymphocytes, 7 per cent monocytes and 1 per cent myelocytes. An hour later a count showed 1,000 white blood cells per cubic millimeter. Because of the intense leukopenia, chemotherapy was discontinued after the single initial dose of sulfathiazole. The sputum, by the direct Neufeld method, was found to contain type II pneumococci. Innumerable colonies of type II pneumococci were grown from the blood. The patient was given 400,000 units of type II antipneumococcus rabbit serum intravenously within seven hours on the evening of admission.

The next day (April 25) the patient's condition became critical. The pneumonic consolidation spread to the upper lobe of the right lung. There were symptoms and signs of pulmonary edema. The patient experienced a chill and a rise of temperature to 104 F. Because of intense dyspnea he was placed in an oxygen tent. A blood count on April 25 showed 700 white blood cells per cubic millimeter. A transfusion of blood was given. Because of the patient's critical state and his failure to respond to large doses of antipneumococcus serum after

TABLE 1.—*Blood Counts and Chemotherapy in Case 1*

| Date | Hemoglobin, per Cent | Leukocytes | Neutrophils, per Cent | Lymphocytes, per Cent | Monocytes, per Cent | Myelocytes, per Cent | Sulfathiazole, Gm. | Sulfapyridine, Gm. |
|---|---|---|---|---|---|---|---|---|
| 4/24 | 70 | 1,400<br>1,000 | 78 | 14 | 7 | 1 | 3 | .. |
| 4/25 | 60 | 700 | 67 | 25 | 5 | 3 | .. | 6 |
| 4/26 | 80 | 5,900 | 84 | 8 | 3 | 5 | .. | 10 |
| 4/27 | 85 | 10,600 | 93 | 5 | 2 | .. | .. | 7 |
| 4/28 | 75 | 23,000 | 95 | 4 | 1 | .. | .. | 7 |
| 4/29 | .. | 28,500 | .. | .. | .. | .. | .. | 7 |
| 4/30 | 64 | 43,600 | 83 | 7 | 5 | 5 | .. | 6 |
| 5/ 1 | 56 | 58,000 | 89 | 5 | 1 | 5 | .. | 6 |
| 5/ 2 | 45 | 35,000 | 81 | 13 | 4 | 2 | .. | 3 |
| 5/ 3 | 51 | 37,200 | 94 | 2 | 4 | .. | .. | .. |
| 5/ 4 | 53 | ..... | .. | .. | .. | .. | .. | .. |
| 5/ 5 | .. | 30,000 | 88 | 12 | .. | .. | .. | .. |
| 5/13 | 46 | 10,400 | 72 | 21 | 7 | .. | .. | .. |

forty-eight hours of hospitalization it was decided to administer sulfapyridine, despite the severe leukopenia. Within twelve hours the patient received 10 Gm. of sodium sulfapyridine intravenously and 7 Gm. orally. Thereafter, 1 Gm. was given orally every three hours. A blood level of 11.5 mg. of sulfapyridine was attained.

Within twenty-four hours after sulfapyridine therapy was begun the patient's general condition improved strikingly. His temperature fell sharply, the maximum on the second day being 101.8 F. A blood count on April 27 showed 5,900 white blood cells, of which 84 per cent were neutrophils, 8 per cent lymphocytes, 3 per cent monocytes and 5 per cent myelocytes. From then on the patient's condition continued to improve. Signs of resolution appeared throughout the right lung. A remarkable leukocytosis developed, the leukocyte count increasing on successive days to 10,000, 23,000, 28,000, 43,000 and finally to a high point of 58,000 six days after the administration of sulfapyridine was begun. Thereafter the leukocyte count fell gradually. On the thirteenth day of the illness evidences of serum sickness and nephritis appeared. These are now disappearing. At the present time the patient has a low grade fever and shows signs of delayed resolution and pleural effusion.

TABLE 2.—*Blood Counts and Chemotherapy in Case 2*

| Date | Hemoglobin, per Cent | Leukocytes | Neutrophils, per Cent | Lymphocytes, per Cent | Monocytes, per Cent | Eosinophils, per Cent | Sulfathiazole, Gm. | Sulfapyridine, Gm. |
|---|---|---|---|---|---|---|---|---|
| 2/25 | 75 | 10,000 | 84 | 16 | .. | .. | 6 | .. |
| 2/26 | 67 | 2,900 | 79 | 14 | 7 | .. | 5 | .. |
| 2/27 | 73 | 6,000 | 70 | 25 | 5 | .. | .. | .. |
| 2/28 | 76 | 6,800 | 78 | 9 | 12 | 1 | .. | .. |
| 2/29 | 71 | 10,900 | 70 | 19 | 9 | 2 | .. | 5 |
| 3/ 1 | 81 | 13,700 | 72 | 20 | 8 | .. | .. | 6 |
| 3/ 2 | .. | 7,600 | 84 | 10 | 4 | 2 | .. | 2 |
| 3/ 3 | .. | ..... | .. | .. | .. | .. | .. | 3 |
| 3/ 4 | 58 | 8,500 | 74 | 16 | 9 | 1 | .. | 7 |
| 3/ 5 | .. | ..... | .. | .. | .. | .. | .. | 5 |
| 3/ 6 | 73 | 11,900 | 64 | 29 | 7 | .. | .. | 4 |
| 3/ 7 | .. | 6,600 | 72 | 20 | 8 | .. | .. | 1½ |
| 3/10 | 68 | 13,700 | .. | .. | .. | .. | .. | 2 |
| 3/11 | 72 | 10,600 | 74 | 20 | 6 | .. | .. | 6 |
| 3/12 | .. | ..... | .. | .. | .. | .. | .. | 4 |
| 3/13 | 72 | 7,000 | 47 | 38 | 12 | 3 | .. | 2 |
| 3/14 | .. | ..... | .. | .. | .. | .. | .. | 2 |
| 3/15 | .. | ..... | .. | .. | .. | .. | .. | 2 |
| 3/16 | .. | ..... | .. | .. | .. | .. | .. | 2 |
| 3/17 | .. | ..... | .. | .. | .. | .. | .. | 2 |
| 3/18 | 75 | 11,100 | 58 | 32 | 8 | 2 | .. | .. |
| 5/ 3 | 80 | 7,850 | 54 | 28 | 11 | 7 | .. | .. |

CASE 2.—A Puerto Rican man aged 66 was admitted to the hospital Feb. 25, 1940. His past history was not relevant. Five days before admission he suffered generalized aches followed by a shaking chill, fever, cough and pain in the chest. He was brought to the hospital because of continued fever, anorexia, thirst, headache, intensified cough and weakness.

On admission the patient's temperature was 103.4 F., respiratory rate 26 and pulse rate 110. There were dulness, diminished breath sounds, focal areas of bronchovesicular breathing and scattered moist rales over the lower lobes of both lungs. The clinical diagnosis was bilateral lower lobe bronchopneumonia or lobar pneumonia.

The next day the patient was completely prostrated. There were frank signs of consolidation over both lower lobes. The sputum revealed type I pneumococci, and innumerable colonies of the same organism were grown from the blood. A blood count on February 25 revealed 10,000 white blood cells per cubic millimeter, of which 84 per cent were neutrophils and 16 per cent lymphocytes. Sulfathiazole therapy was begun. The next day, after 11 Gm. of sulfathiazole had been administered, the patient was found to have 2,900 white blood cells per cubic millimeter, with 79 per cent neutrophils. Because of the leukopenia, sulfathiazole was discontinued, and 400,000 units of type I rabbit antipneumococcus serum was given intravenously.

On February 29 the patient's condition appeared worse, despite specific therapy. The signs in his lungs became more extensive. Because the prognosis seemed extremely unfavorable and because the leukocyte count had risen to 10,900 per cubic millimeter, sulfapyridine therapy was begun in doses of 1 Gm. every four hours. Within twenty-four hours, the patient's temperature fell precipitously, and his clinical condition improved rapidly. After an initial rise to 13,700 the leukocyte count fell to 7,600 and then varied between 12,000 and 6,700 per cubic millimeter. The pneumonia cleared rapidly, but the patient's stay in the hospital was protracted because of pain in the lower portion of the back and spikes of fever, which were later found to be due to an inflammatory lesion of the lumbosacral region of the spine, probably a pneumococcic osteomyelitis. Before the patient left the hospital he was again given 11 Gm. of sulfathiazole in divided doses, as on admission, to determine the presence of a special sensitivity to this drug, but there was no effect on his blood count.

### COMMENT

In both cases the patients were critically ill; they had failed to respond to specific pneumococcus antiserum, and their clinical improvement may be fairly attributed to the use of sulfapyridine. Many of the elements in both cases are those associated generally with a high mortality, viz. the multiplicity of lobes involved, the bacteremia, the extreme number of colonies in the blood cultures, the leukopenia, the poor clinical condition and, in the second case, the advanced age of the patient.

The severity of the infection supports the interpretation that the leukopenia in these cases was due to pneumonia and pneumococcic bacteremia. There was no history of the ingestion of drugs which might have caused leukopenia before admission to the hospital. In the first case the prolonged and excessive consumption of alcohol may have damaged the bone marrow and predisposed the patient to leukopenia, as suggested by Samuels and Lambert.[3] The single dose of sulfathiazole given to the first patient, almost simultaneously with the first examination of the blood, may be dismissed as a causative factor. The second patient was given a total of 11 Gm. of sulfathiazole in one day. However, this patient's leukocyte count was only 10,000 (a relative leukopenia for a patient with pneumonia) even before the sulfathiazole was given. The total dose of sulfathiazole was too small and the period of administration too brief to cause the drop to 2,900 white blood cells, if one can draw any conclusions from experiences with sulfapyridine. Furthermore, a special sensitivity to sulfathiazole seemed unlikely, since the drug produced no effect on the patient's blood count when administered again in the same dose.

The observations in the foregoing cases indicate that the presence of leukopenia is no contraindication to the use of sulfapyridine in the treatment of lobar pneumonia. The rise in the white blood count after sulfapyridine administration was due to the control of the severe infection which was the cause of the original leukopenia. There have been three reports of somewhat analogous cases in which sulfanilamide was therapeutically helpful in the treatment of streptococcic infections associated with granulocytopenia due either to the infections or to the ingestion of aminopyrine. Since the presence of a low leukocyte count in patients with lobar pneumonia is usually associated with a relatively more severe infection and a higher mortality than in persons with leukocytosis, and since sulfapyridine is the most effective single therapeutic agent in the treatment of lobar pneumonia, leukopenia seems to be a special indication for the use of this drug in the therapy of lobar pneumonia.

### SUMMARY

1. The two cases of acute lobar pneumonia here reported presented severe leukopenia, the white blood cells numbering as low as 700 and 2,900 per cubic millimeter respectively.

2. In both cases, multiple lobes were involved; there was intense bacteremia, and the clinical condition was desperate despite the use of huge doses of type-specific antipneumococcus serum.

3. After the administration of sulfapyridine there was a prompt improvement in the clinical picture with a subsequent favorable course. The leukocyte count rose progressively and in one case reached 58,000 per cubic millimeter before regressing toward normal.

3. Samuels, S. S., and Lambert, R. A.: Relationship of the Leukocyte Count and Bone Marrow Changes in Acute Lobar Pneumonia, J. Infect. Dis. **23**: 443 (Nov.) 1918.

### CONCLUSION

The presence of leukopenia in cases of acute lobar pneumonia does not contraindicate the administration of sulfapyridine. In fact, when lobar pneumonia is associated with leukopenia sulfapyridine therapy is especially indicated, because such cases usually represent severe pneumonic infections with a relatively high mortality.

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## SULFANILAMIDE IN THE THERAPY OF ACTINOMYCOSIS

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Chemotherapeutic successes in the field of bacterial and protozoal infections have not yet been equaled in the virus or fungus groups. Of the virus infections, only venereal lymphogranuloma and trachoma have seemed responsive to sulfanilamide. There have been relatively few reports of the effect of sulfanilamide in fungous infections.

Six clinical reports have mentioned the use of sulfanilamide or related compounds in actinomycosis, and one report describes a trial of the drug in an experimental infection. The earliest of these was that of Walker,[1] who in 1938 reported a case of abdominal actinomycosis arising from the appendix, which healed quickly after two courses of sulfanilamide. The first course lasted six days and the second five days, with an interval of ten days. The dosage was 1 Gm. three times a day throughout. Compound solution of iodine and potassium iodide had been given previously without effect.

Bailey,[2] also in 1938, reported a case in which potassium iodide, sodium iodide intravenously, thymol and sulfanilamide were administered. The report, made while the patient was still in the hospital, stated that he was improved but not well. The dosage of sulfanilamide was not mentioned.

Miller and Fell[3] reported a case in which a mass in the lower part of the abdomen of a boy proved on incision to be actinomycotic. Thymol and potassium iodide were given orally, thymol in oil applied locally, and roentgen irradiation given as well, over a period of four months. The patient lost strength and the abdominal mass grew larger, however, and sulfanilamide was started in small doses, 0.65 Gm. three times a day. This was continued for ten months with apparently complete recovery.

Ogilvie[4] recently reported a case of actinomycosis probably arising in the appendix and involving a large part of the anterior abdominal wall. Despite surgical opening of the sinuses and long continued administration of iodide, the infection advanced. Sulfapyridine, 2 tablets six hourly (this probably being 4 Gm. a day),

From the Departments of Surgery and Pharmacology of the Stanford University School of Medicine.

1. Walker, O.: Sulfanilamide in the Treatment of Actinomycosis, Lancet **1**: 1219 (May 28) 1938.

2. Bailey, W. H.: A Case of Actinomycosis in Man, J. Oklahoma M. A. **31**: 339 (Oct.) 1938.

3. Miller, E. M., and Fell, E. H.: Sulfanilamide Therapy in Actinomycosis, J. A. M. A. **112**: 731 (Feb. 25) 1939.

4. Ogilvie, W. H.: Abdominal Actinomycosis Treated with Sulfapyridine, Brit. M. J. **2**: 254 (Aug. 24) 1940.

was given with dramatic and permanent recovery. The drug was given for only thirteen days, average blood levels being 2 mg. per hundred cubic centimeters for the free drug and 3.3 mg. per hundred cubic centimeters for the total drug. The author suggests that the action of the drug was largely against the coincidental streptococcic infection and that the cure of the actinomycosis then resulted from natural processes.

Sudler and Johnson [5] recently reported two cases of actinomycosis of the jaw treated successfully with sulfanilamide. One of the patients was getting worse while on iodides and roentgen treatments and then healed promptly after two short courses of sulfanilamide. The second patient was treated with sulfanilamide alone.

Morton [6] reported 3 cases of actinomycosis, in 2 of which sulfanilamide was administered. In 1 there was involvement of the jaw, face, meninges and brain, and death occurred although sulfanilamide was given at one time for a period of a month in doses of 4 Gm. daily. In the other case there was actinomycosis of the breast and axilla, and sulfanilamide was given intermittently for about six weeks in doses of 4 to 8 Gm. daily, with blood levels of 4 to 8 mg. per hundred cubic centimeters. At the time of the report the patient was improved but not well. Both of these patients had iodides, roentgen rays and vaccine injections, as well as sulfanilamide, and the patient who died also had thymol applied locally.

The experimental report was that of Hemmens and Dack,[7] who found that they could cure otherwise fatal infections of rabbits with Bacterium necrophorum, an organism distantly related to Actinomycosis bovis, by early and persistent treatment with sulfanilamide.

These favorable reports are in considerable contrast to the conclusion of Good,[8] who in 1931 reported 62 cases of abdominal actinomycosis. Treatment consisted of free drainage, potassium iodide, general upbuilding and radium or roentgen irradiation. Only 8 were apparently cured, and it was concluded that the results were generally poor. More recently another report from the Mayo Clinic by Masson [9] included 2 cases treated with roentgen rays and small doses of iodide, with complete recovery. Mention is made of another fatal case, however.

We are reporting three cases of actinomycosis, one of the jaw, one of the chest and one of the abdomen, all completely cured, in which the administration of sulfanilamide seemed to be the deciding therapeutic agent.

## REPORT OF CASES

CASE 1.—S. K., a barber aged 65, entered Stanford Hospital on Sept. 30, 1937 for a swollen and painful jaw of three months' duration. Two teeth in the lower jaw had been removed in July in a fruitless effort to correct the pain, followed by an increasing swelling of the right face. There was no history of contact with possible sources of mycotic infection.

Physical examination revealed an extensive swelling of the right side of the face from the temporal fossa to the submaxillary region (fig. 1 *A*). This swelling was quite hard except for a small area of fluctuation immediately over the malar bone. The patient was unable to open the jaw more than ⅛ inch. A roentgenogram disclosed several areas of bone destruction of the right mandible, one area opening into the open alveolus from which the right second molar had been removed.

The Wassermann reaction was negative. The red cells numbered 3,600,000, the white cells 14,000, of which 73 per cent were neutrophils (1 per cent banded), 21 per cent lymphocytes and 6 per cent monocytes. The hemoglobin was 67 per cent of normal. The urine was normal.

On October 4 a short incision was made over the fluctuant area, evacuating a light, thin pus containing numerous grayish yellow granules. Actinomycosis was suspected and subsequently proved by studies of a smear, culture and tissue sections. A clamp introduced through the malar incision dropped into an abscess cavity around the mandible. A counter incision was made at the angle of the jaw.

Roentgen treatment to the right side of the face was administered on October 6 and 7 for a total of 500 roentgens and again on November 10 and 11 for a total of 500 roentgens. Potassium iodide was given in increasing amounts until the

Fig. 1 (case 1).—Appearance of patient: *A*, Oct. 5, 1937, before treatment; *B*, Feb. 16, 1940, after treatment.

patient was getting 12 Gm. daily. Ferrous sulfate, halibut liver oil and brewers' yeast supplemented the diet.

Improvement was slight and on November 16, because of inadequate drainage, the previously made wounds were enlarged and connected with a spontaneously developed opening anterior to the angle of the jaw. Bare mandible was revealed in the wound. Intractable pain followed this procedure. On November 23 sulfanilamide was begun 1 Gm. every six hours, and an almost immediate reduction in pain occurred.

Within three days there was visible improvement in the wound, the redness of the skin and the induration being markedly lessened and the discharge decreased. Within ten days a sinus which had burst through the skin spontaneously only ten days before the administration of the sulfanilamide had practically healed, and the patient was sleeping without sedatives. On December 8 the sulfanilamide was discontinued. On this date there was very little discharge, induration had practically disappeared, and the patient was able to open his mouth fully 2 cm.

By December 15, induration had again set in and pus in which sulfur granules were easily demonstrated was again obtained from the wounds. Again sulfanilamide, 1 Gm. every six hours,

5. Sudler, M. T., and Johnson, C. B.: Treatment of Actinomycosis with Sulfanilamide, J. Kansas M. Soc. **40**: 330 (Aug.) 1939.
6. Morton, H. S.: Actinomycosis, Canad. M. A. J. **42**: 231 (March) 1940.
7. Hemmens, E. S., and Dack, G. M.: Effect of Sulfanilamide on Experimental Infections with Bacterium Necrophorum in Rabbits, J. Infect. Dis. **64**: 43-48 (Jan.-Feb.) 1939.
8. Good, L. P.: Actinomycosis of the Abdomen, Arch. Surg. **22**: 307 (Feb.) 1931.
9. Masson, D. M.: Abdominal Actinomycosis: Report of Two Cases with Clinical Cure, Proc. Staff Meet., Mayo Clin. **11**: 833 (Dec. 30) 1936.

was administered, and on December 31 the patient was discharged from the hospital with draining sinuses but practically no swelling of the face.

Owing to a widespread dermatitis, the sulfanilamide was discontinued on January 5 and potassium iodide was again given. Small beads of pus could occasionally be expressed from the sinuses, which invariably contained a few sulfur granules. On February 15 and 16 roentgen treatments for a total of 500 roentgens were again administered, and again on May 9 and 10.

In July the patient returned with a small abscess in the temporal region from which a half ounce of pus was evacuated, but Actinomyces was not present. Healing was complete on Aug. 1, 1939. When last seen, in January 1940, the patient was still perfectly healed and well (fig. 1 *B*).

CASE 2.—E. Z., a student aged 24, in March 1939 felt pain in the right side of his neck and chest, which was worse on motion. Three months later, roentgen examination of the chest showed density in the right upper lobe, and a swelling appeared medial to the right scapula which on incision yielded pus containing Actinomyces.

On admission at this time he was referred by his physician in the Woodland Clinic to the Stanford Medical Service for further care. He was febrile and somewhat prostrated. In addition to the draining sinus near the scapula and impaired physical signs over the right upper chest, the liver and spleen were palpable. The patient was moderately anemic, with a red count of 3.5 million and a hemoglobin of 53 per cent Sahli. The white blood cell count was 10,000, with a normal differential. The urine and stool were not remarkable, the blood Wassermann reaction was negative, and the sedimentation rate was 26 mm. per hour, corrected. Roentgen examination of the chest showed density in the upper half of the right lung field (fig. 2 *A*).

The patient was immediately started on sulfanilamide, 6 Gm. daily, which was continued for eight days. At this time the smear from the draining sinus had become negative for Actinomyces, and the patient felt better, but his temperature, which had receded to normal, again rose. For this reason the sulfanilamide was reduced to 4 Gm. daily for two days, then discontinued for three days. Six Gm. daily was then given for another week. Sodium iodide was given during the next month in increasing doses until he was taking 4 Gm. daily. In the meantime he was treated generally with a high calory diet, vitamins, ferrous sulfate and three transfusions. The sinus stopped draining entirely two weeks after the sulfanilamide was stopped, and one month later the patient was dismissed, apparently nearly well, although the roentgen appearances in the right upper lung field were little changed. His hemoglobin at this time was 78

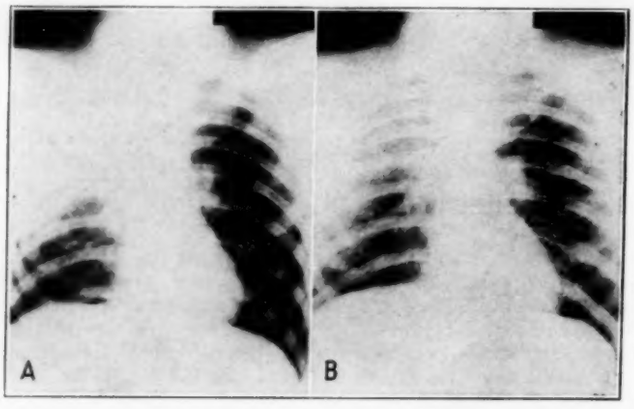


Fig. 2 (case 2).—*A*, density in the upper half of the right lung field, June 5, 1939; *B*, decrease in the density, Dec. 14, 1939.

per cent Sahli, his white blood cell count 8,700, and sedimentation rate 20 mm. per hour, corrected. He was seen at intervals thereafter, five months later feeling well, with a sedimentation rate of 7 mm. per hour, and with roentgen evidence of only a little density in the right lung (fig. 2 *B*). The last report, a year after the onset of the infection, states that he seemed entirely well.

CASE 3.—A 12 year old Japanese schoolboy bumped the lower right part of his abdomen on the corner of a table on Nov. 10, 1939. The area continued to be tender and on December 1 a hard lump could be felt beneath the lower right rectus muscle. The possibility of a subfascial hematoma was considered by his local physician, Dr. George R. Sasaki, of Salinas, Calif., but a diagnostic puncture obtained no blood or pus from the mass. On December 8 Dr. Sasaki made an incision along the lateral

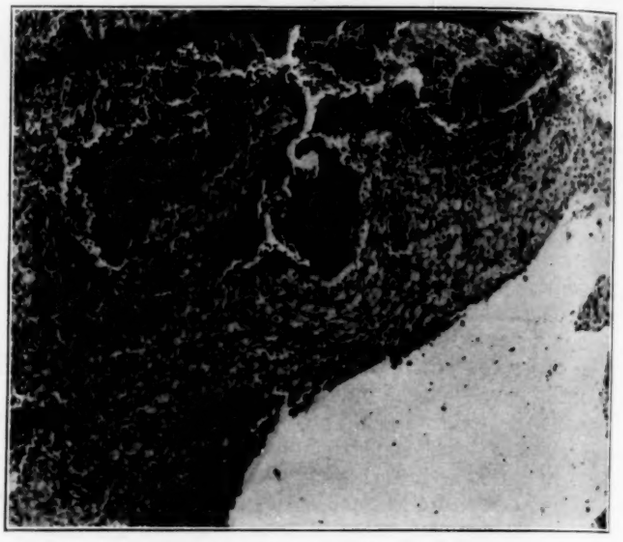

Fig. 3 (case 3).—Section showing ray fungi; reduced from a photomicrograph with a magnification of 100 diameters.

border of the rectus muscle exposing a large, firm mass which contained small areas of necrosis. Microscopic examination (fig. 3) by Dr. James B. McNaught, of the Stanford Department of Pathology, showed the tissue to contain the ray fungus of actinomycosis. Iodides were started but the wound continued to drain thick yellow pus. On December 17 the boy developed a marked cystitis. On December 21 he was brought to Stanford Hospital.

On admission he was pale and weak. The abdomen showed thick yellow pus draining from two granulating sinuses near the center of a lower right rectus scar (fig. 4 *A*). On palpation there was a stony hard, tender, fixed mass in the right lower quadrant measuring 9 by 7 cm. On rectal examination a tender mass could be felt anteriorly which largely filled the pelvis.

The laboratory studies showed a slight secondary anemia with 4,640,000 red blood cells with 80 per cent hemoglobin, and 18,400 leukocytes with 80 per cent polymorphonuclears, 3 per cent eosinophils and 17 per cent lymphocytes. The urine showed a heavy cloud of albumin with a few red blood cells and 40 to 50 leukocytes per high power field.

Sulfanilamide was immediately started, beginning with 0.5 Gm. every four hours, with sodium bicarbonate 0.5 Gm. every four hours. On the following day the dose of sulfanilamide was increased to 0.75 Gm. every four hours (total 4.5 Gm. daily). A blood sulfanilamide determination on the day following admission, December 22, showed free blood sulfanilamide to be 4.0 mg. per hundred cubic centimeters and total 5.6 mg. On December 23 free blood sulfanilamide was 8.2 mg. per hundred cubic centimeters, total 10.4 mg., and on December 24 free blood sulfanilamide was 9.2 mg. per hundred cubic centimeters and total 11.4 mg., as included in figure 5.

The cystitis subsided rapidly after the sulfanilamide was started. Within twenty-four hours the marked frequency and burning on urination had decreased and within forty-eight hours the urine was practically clear. The drainage from the abdominal sinuses diminished rapidly and within one week the abdominal mass was measurably smaller. On Jan. 3, 1940, an abscess pointing at the umbilicus was incised and drained. The pus contained long filamentous branching gram-positive rods and typical sulfur granules. By January 10 the pelvic mass, which had been felt by rectum, was no longer palpable.

The hemoglobin dropped from 80 per cent to 65 per cent on December 29. The temperature, which on admission was 37.8 C. (100 F.) rectally, started to rise on December 26 and rose to

39.8 C. (103.6 F.) on December 29. It was felt that the high fever may have been due to the effect of the sulfanilamide, so it was discontinued on December 29. The temperature came down promptly with no other change in therapy and became normal within twenty-four hours. On Jan. 2, 1940, four days after the sulfanilamide was stopped, the hemoglobin had risen to 69 per cent. On January 2 the sulfanilamide was again started, 0.75 Gm. being given every four hours, and this dose was continued until January 16, when the dose was dropped to 0.5 Gm. every four hours.

The abdominal mass slowly decreased in size and the drainage lessened between December 21 and January 7 and then for several days seemed about stationary. On January 12, sodium iodide was started, 1 Gm. being given three times daily. On January 13, roentgen treatment was started, eleven treatments of 50 roentgens each being directed to the right lower part of the abdomen (January 13, 20, 27, 31, February 3, 6, 10, 14, 17, 21, 24 to a total of 715 roentgens).

The sodium iodide was administered for two days. On the second day the patient again started having a fever; the temperature reached 39 C. (102.2 F.). This febrile reaction was believed to be due to the sudden liberation of toxic material from the abscess from the action of the sodium iodide, so the iodide was stopped. On February 8, sodium iodide was again started, gradually being increased to 1 Gm. three times daily, which was continued throughout his stay in the hospital.

Additional therapy included a high caloric, high vitamin diet and 0.2 Gm. of ferrous sulfate four times daily. On this regimen the mass continued to diminish in size, the sinuses healed and the patient's appetite and strength increased. The blood count improved, rising to 87 per cent hemoglobin before the patient's dismissal. He also gained 10 pounds (4.5 Kg.) during his stay in the hospital. On dismissal on March 21, three months after admission, there was no mass palpable in the abdomen.

The patient was kept on sulfanilamide 0.5 Gm. every four hours and 1 Gm. sodium iodide daily for one month after dismissal. Two months after dismissal a small furuncle developed in the scar, and although it appeared to be superficial it was decided to start sulfanilamide again. The patient was put on 0.3 Gm. of sulfanilamide four times daily and 1 Gm. of sodium iodide three times daily. This dosage was continued for another month. Within three days the infection had healed. The patient was last seen on Dec. 20, 1940, ten months after dismissal. He was well and there was no evidence of residual actinomycosis (fig. 4 *B*). The clinical course is summarized in figure 5.

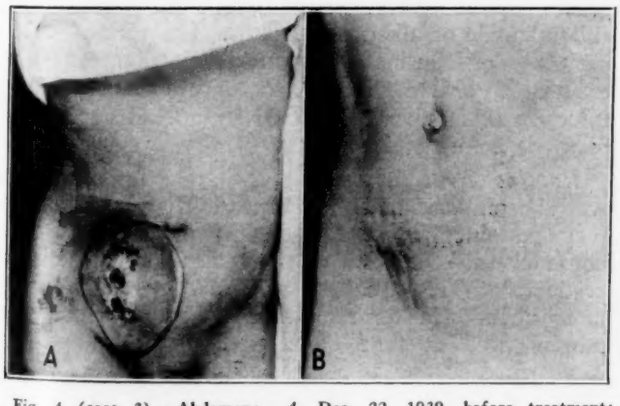


Fig. 4 (case 3).—Abdomen: *A*, Dec. 22, 1939, before treatment; *B*, Sept. 24, 1940, after treatment.

## COMMENT

The cases reported detail the apparently complete cures of a man with actinomycosis of the jaw, another with involvement of the lung and rib cage, and a boy with serious and extensive abdominal actinomycosis. Sulfanilamide was used in all three cases.

Although it has been suggested that the effect of sulfanilamide is merely to combat secondary invaders in the abscesses and sinuses, allowing the natural bodily resistance to overcome the fungus, the rapid and complete recoveries reported in the literature and the striking responses in our cases suggest that there may be a direct effect as well. This view is to some extent

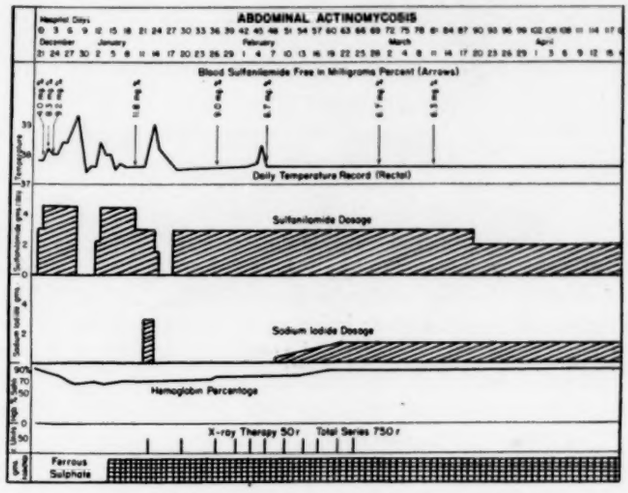


Fig. 5 (case 3).—Clinical course while patient was under treatment.

supplemented by the reported effectiveness of sulfanilamide on an experimental infection with an organism related to Actinomycosis bovis. However, in our case of abdominal actinomycosis the lesion remained roughly stationary after about a month of treatment with sulfanilamide and then regressed completely after further sulfanilamide and the addition of iodides and roentgen rays. This suggests that the principal effect during the early stages of treatment was on the secondary invaders and that other factors were important in the final cure. It is impossible to be definite on this point in the absence of in vitro studies or experimental pure culture infections.

There are several incidental points of interest. Over the first two weeks of the sulfanilamide course in case 3 there was a gradually progressing secondary anemia. Despite continuance of the sulfanilamide, and perhaps aided by the ferrous sulfate, this disappeared, so that the hemoglobin was normal on the patient's dismissal. It is reassuring to know that the slow anemia can, at least at times, be completely controlled while the drug is still being administered. Adaptation of the blood forming system to the drug may well have been more important than the iron therapy. Two of the patients had what was interpreted as episodes of drug fever, yet therapy was continued after short intermissions without untoward results. Another spike of fever coincided with the abrupt administration of a large dose of sodium iodide (3 Gm. daily) and possibly was due to absorption of liquefied toxic substances from the granuloma. When repeated later in smaller, ascending doses, there was no recurrence of this toxic sign.

## CONCLUSIONS

Three cases of actinomycosis, one of the jaw, one of the lungs and rib cage, and one of the abdomen, have been apparently completely cured. Therapy included the use of sulfanilamide, iodides and roentgen rays. In view of the serious nature of this infection and the apparent value of sulfanilamide, this or a related drug should be included in the treatment of actinomycosis.

Sacramento and Webster streets.

# THE CHEMOTHERAPY OF GONOCOCCIC INFECTIONS

## I. SUMMARY OF EXPERIENCE WITH SULFANILAMIDE

## II. INVESTIGATION OF CHEMOTHERAPEUTIC EFFECT OF SULFAPYRIDINE

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Previous reports by us [1] have presented the results of studies dealing with the use of sulfanilamide in the treatment of gonococcic infections. In the present paper it is desired to set forth the results of a similar investigation of sulfapyridine and to compare the adaptability of sulfanilamide and sulfapyridine therapy to the treatment needs of the disease.

### I. SUMMARY OF EXPERIENCE WITH SULFANILAMIDE

Our efforts during 1937 and 1938 were concentrated on studies of sulfanilamide therapy in gonococcic infections of approximately 1,800 hospitalized male and female patients. Under ideal conditions sulfanilamide proved to be a valuable agent in the treatment of this disease. By means of large doses (1.3 Gm.) of sulfanilamide given at four hour intervals during both day and night, it was possible to effect a high percentage of cures. Although serious toxic effects did not occur in the series, it is well recognized that the character of toxic manifestations restricted full therapeutic dosages of sulfanilamide, especially in outpatients, and consequently lessened its value as a means of reducing significantly the incidence of the disease. From the information gained from that series, which was reported previously, the following conclusions were drawn:

1. When consideration is given to the duration of the infection there is little if any difference in the curative response of male or female patients.

2. Higher blood concentrations of free sulfanilamide approximating 9 to 11 mg. per hundred cubic centimeters appear to be more effective in producing cures than lower levels of 3 to 6 mg. per hundred cubic centimeters. Cures and failures occur at both levels, however.

3. The exaggeration of the toxic manifestations occasioned by the large doses necessary to produce and maintain the higher concentration in the blood suggests the advisability of hospitalization at least during the period of intensive therapy.

4. Prolonged administration of sulfanilamide is contraindicated. If a favorable therapeutic response is not obtained by the fifth or sixth day, it is not likely to occur. Even with a curative response it is not advisable to continue sulfanilamide beyond the tenth or twelfth day. The prolonged administration even of small doses of sulfanilamide appears to act as the etiologic factor in the production of granulocytopenia.

5. If sulfanilamide is given early in the course of gonorrhea, if it is given in small doses or, particularly, if given both early and in small doses it is productive of a low cure rate and apparently establishes in many failures a condition simulating a "sulfanilamide resistant" infection.

6. A febrile response of 100.8 F. or over, occasioned by sulfanilamide therapy, is an indication to suspend or decrease the amount of sulfanilamide.

7. The dosage of sulfanilamide cannot be routinized. Adequate dosage of the individual patient should be decided daily on the basis of laboratory findings and sound clinical judgment.

8. Sulfanilamide is capable of producing a subclinical state of gonococcic infection in which, for a time, the disease may be completely asymptomatic and which may be detected only by finding the gonococcus on spread or culture examination. Prolonged observation of the patient is important, especially where reliable cultural investigations are not freely accessible.

9. Sulfanilamide is a powerful chemotherapeutic agent which should be used only under continuous and competent medical supervision.

10. An immune mechanism may be essential for the most efficient action of sulfanilamide. This hypothesis receives support from the fact that the cure rate increases when sulfanilamide treatment is delayed. This result is portrayed graphically in the accompanying charts.

### II. INVESTIGATION OF CHEMOTHERAPEUTIC EFFECT OF SULFAPYRIDINE

*Material.*—In a series of 300 cases under report, there are 200 male and 10 female patients who were hospitalized and 81 men and 9 women who were treated as outpatients. Not any of the hospitalized or outpatient women had had previous chemotherapy. Among the men, however, there were 136 inpatients and 30 outpatients who had been treated elsewhere and had failed to respond to one or more therapeutic attempts with sulfanilamide or allied compounds. The series is representative of routine admissions, selection not being exercised. Every patient had an obvious gonococcic infection which was confirmed by spread and culture methods before sulfapyridine therapy was started.

*Routine Procedure.*—The 200 male patients who were hospitalized received the usual clinical and laboratory examinations and hospital care. They were not confined to bed. For a time the fluid intake was restricted to 1,500 cc. a day, but this limitation was later abandoned as nonessential. Sulfapyridine was administered at four hour intervals night and day. Daily spreads and two glass urine tests were carried out. The carbon dioxide combining power of the blood plasma was followed in 27 patients. On complete relief of symptoms, negative findings in spreads, cessation of discharge and clearing of the two glass urine test, a moderately sized urethral sound was passed and the penile urethra massaged. The resulting material, together with that secured from prostatic massage, was subjected to spread and culture examination. The spread and culture studies were repeated on an average of more than six occasions. Concentration and excretion studies in the present series, as well as those

From the Venereal Disease Research Laboratory.

1. Van Slyke, C. J.; Thayer, J. D., and Mahoney, J. F.: Sulfanilamide Therapy in Gonococcal Infections, Ven. Dis. Inform. **18**: 417, 1937. Mahoney, J. F.; Van Slyke, C. J., and Thayer, J. D.: Sulfanilamide in Hospitalized Gonorrhea, Am. J. Syph., Gonor. & Ven. Dis. **22**: 691, 1938. Van Slyke, C. J., and Mahoney, J. F.: Further Observations in Sulfanilamide Therapy of Gonococcal Infections, New York State J. Med. **40**: 122, 1940. Nimelman, Anna; Mahoney, J. F., and Van Slyke, C. J.: Sulfanilamide Therapy of Gonococcal Infection in Hospitalized Prostitutes: The Gonococcus and Gonococcal Infection, New York, Science Press, 1939, p. 132.

reported by Long and Feinstone,[2] have shown that sulfapyridine is not demonstrable in the body fluids at the end of three or four days. Therefore a special effort was made to secure as many culture studies as possible beginning five days after the discontinuance of medication, in order to obviate the possible inhibiting influence of sulfapyridine on the growth of gonococci in cultures.

If repeated physical examinations, two glass urine tests and spread and culture studies failed to reveal evidence of residual gonococcic infection, the patient was considered apparently cured and discharged from the hospital. All were advised to return at frequent intervals for posttreatment observation and to reenter the hospital in the event of recurring symptoms. Sexual intercourse with the protection of a condom, or the moderate use of alcoholic beverages, was not interdicted. Satisfactory clinical response and repeated failure to demonstrate the causative organism in material obtained by urethral and prostatic massage constituted the essential criteria of apparent cure.

The 10 female patients who were hospitalized received comparable care, except that sulfapyridine in smaller doses was given only four times a day at four hour intervals. The criteria of apparent cure in hospitalized women demanded:

1. Disappearance of purulent discharge from the urethra and cervix, together with cessation of clinical evidence of specific infection.
2. Evidence of satisfactory recession of adnexal involvement.
3. Negative findings in repeated spread and culture examinations.

The 81 male and 9 female patients who received sulfapyridine on an outpatient basis were likewise subjected to prolonged spread and culture studies in addition to urinalyses, hemoglobin determinations, white cell counts and determinations of free and total blood sulfapyridine. Usually these patients were seen three times during the first week, twice during the second week and then weekly thereafter. They were instructed to take sulfapyridine four times daily at four hour intervals, i. e., at 8 a. m., 12 noon, 4 p. m. and 8 p. m. The criteria of cure were the same as stated for the hospitalized patients, and a minimum of three negative

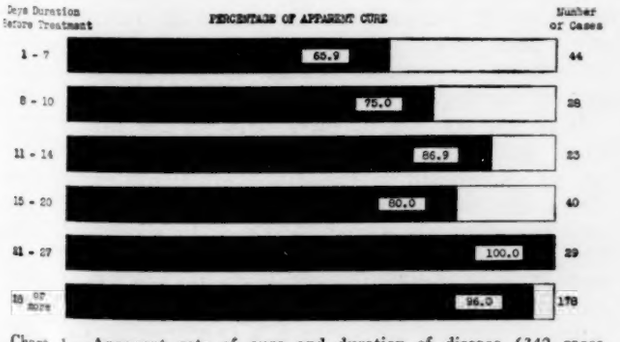


Chart 1.—Apparent rate of cure and duration of disease (342 cases, 219 men and 123 women).

cultures was obtained. It has been possible to follow some of these patients through as many as fifteen culture examinations.

*Bacteriologic Methods.*—Urethral, prostatic and cervical secretions were collected in carrying tubes of Torrey and Buckell's C medium, from which plates of both Douglas chocolate agar and the Difco medium for gonococci were inoculated. Incubation was carried out at 35 C. under an atmospheric tension of 10 per cent carbon dioxide. The plates were inspected at the expiration of forty-eight hours. The oxidase reaction was employed as a partial confirmatory procedure, but differentiation in questionable instances was based on the fermentation reactions. The staining method of Gram as recommended by Carpenter[3] was followed.

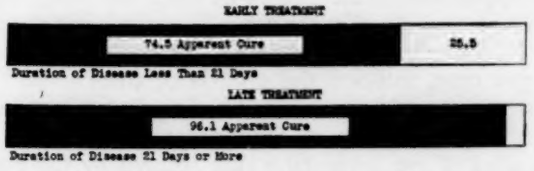


Chart 2.—Apparent rates of cure in early and late treatment (342 cases, 219 men and 123 women).

*Dosage.*—The usual dosage for the 200 hospitalized men was 6 Gm. a day for two days and 3 Gm. a day for an additional four to six days. The daily dosage was given in equally divided amounts at four hour intervals.

The usual dosage for all outpatients and for the hospitalized women was 3 Gm. for the first day and 2 Gm. daily for an additional six to nine days. The daily dosage for the outpatients and hospitalized women was prescribed in four equally divided doses to be taken only during the day.

TABLE 1.—*Patient Groups and Dosage Employed*

| Number of Patients | Usual Dosage | Maximum Total Dosage | Minimum Total Dosage |
|---|---|---|---|
| Hospitalized men.....200 | 6.0 Gm. 2 days 3.0 Gm. 4-6 days | 57.0 Gm. in 12 days (failure) | 16.5 Gm. in 5 days (cure) |
| Hospitalized women.... 10 | 3.0 Gm. 1 day 2.0 Gm. 6-9 days | 33.0 Gm. in 10 days (failure) | 10.0 Gm. in 3 days (cure) |
| Outpatient women..... 9 | | | |
| Outpatient men..... 81 | | | |

The various groups considered and the respective dosages employed are given in table 1.

*Results of Sulfapyridine Therapy.*—Of the 136 patients who had previously failed to respond to doses of sulfanilamide (administered for one or more therapeutic attempts), 103, or 75.7 per cent, were provisionally discharged as cured. Of this group 6 had also failed to be cured after two to six sessions of induced hyperpyrexia and 4 had failed to benefit from the administration of sulfanilyl-sulfanilamide (di-sulfanilamide).

Fifty-six, or 87.5 per cent, of the 64 hospitalized male patients who had not received chemotherapy before the institution of sulfapyridine treatment were discharged as apparently cured.

Nine of the 10 women who were hospitalized attained clinical and bacteriologic cures. The 1 in whom failure occurred was intolerant of the drug and received only 1.5 Gm. during a period of eight hours. This amount, however, quickly relieved the severe abdominal pain produced by an extension of the infection.

Of the 81 outpatient men, 10 lapsed treatment before completing medication or a suitable period of posttreatment observation and were not considered in

2. Long, P. H., and Feinstone, H. W.: Observations upon the Absorption and Excretion of Sulfapyridine (2-Sulfanilyl Aminopyridine), Proc. Soc. Exper. Biol. & Med. **39**: 486, 1938.

3. Carpenter, C. M.: Report of Laboratory and Research Committee, Tr. Am. Neisserian M. Soc., 1936, p. 55.

determining the cure rate. Prior to the lapse it was noted that each of these patients received an immediate favorable therapeutic response which seemed to indicate a successful outcome, particularly since a definite failure is usually apparent after five or six days of medication.

The remaining 71 patients of this group of outpatient men are divided into two sections. One section of 29 patients had failed previously to respond to sulfanilamide therapy, but 20, or 68.9 per cent, of these satisfactorily answered the proofs of cure following sulfapyridine treatment. In the second section of 42 patients who had not received previous chemotherapy 36, or 85.7 per cent, satisfied the criteria of cure.

Cures were obtained in all 9 female patients who received sulfapyridine as outpatients.

Because of the lower cure rate secured by the use of sulfapyridine in those cases which had previously failed to respond to sulfanilamide or allied compounds, a gross cure rate is not considered, as it would naturally vary depending on the percentage of sulfanilamide failures in the group.

TABLE 2.—*Results of Sulfapyridine Therapy in Gonococcic Infections*

| Number of Patients | Dosage | Previous Sulfanilamide Therapy | Number Cured | Percentage Cured | No Previous Sulfanilamide Therapy | Number Cured | Percentage Cured |
|---|---|---|---|---|---|---|---|
| Hospitalized men..... 200 | 6 Gm.-2 days 3 Gm.-4-6 days | 136 | 103 | 75.7 | 64 | 56 | 87.5 |
| Hospitalized women..... 10 | 3 Gm.-1 day 2 Gm.-6-9 days | None | ... | .... | 10 | 9 | 90.0 |
| Outpatient women..... 9 | 3 Gm.-1 day 2 Gm.-6-9 days | None | ... | .... | 9 | 9 | 100.0 |
| Outpatient men..... 71 | 3 Gm.-1 day 2 Gm.-6-9 days | 29 | 20 | 68.9 | 42 | 36 | 85.7 |
| Total..... 290 | ..... | 165 | 123 | 74.5 | 125 | 110 | 88.0 |

The duration of the disease before institution of sulfapyridine therapy apparently did not influence the effectiveness of the treatment.

The male patients who responded favorably experienced rapid subsidence of symptoms and disappearance or decrease of the urethral discharge to a slight amount of meatal moisture within an average of two and five-tenths days. Urethral spreads became negative for gonococci within an average of one and four-tenths days, but it was not exceptional to find occasional extracellular gram-negative diplococci in a few subsequent examinations.

The bacteriologic response and relief of subjective symptoms was equally good in women, although the objective symptoms of the infection disappeared somewhat more slowly.

Practically all the patients who failed to satisfy the criteria of cure displayed an initial response consisting of decrease of discharge and lessening of subjective symptoms. Although the clinical improvement continued in a portion of this group, there were always sufficient clinical signs to warn of the presence of the infection within six days after discontinuance of medication. There was not any instance of extension of the disease during treatment, even among the failures. No common factor was discernible to which the failures could be attributed.

Table 2 summarizes the results of sulfapyridine therapy in gonococcic infections.

*Results in Complicated Cases.*—There did not appear to be any appreciable difference in the response of complications of gonococcic infections between the hospitalized patients who received the larger doses of sulfapyridine and the outpatients who received the smaller doses.

Unilateral epididymitis was observed in 4 hospitalized and 2 outpatients. In each case the pain was entirely relieved within twenty-four to thirty-six hours and the swelling subsided within three to ten days.

Two cases of acute gonococcic arthritis were observed in the hospitalized group. One man displayed redness and swelling of the wrist and ankle, which was accompanied by severe pain. The pain was entirely relieved in five days, the swelling disappeared and complete physiologic function was restored within an additional five days. The other experienced intense pain and effusion of the knee joint. Under sulfapyridine therapy the pain was relieved on the second day and the knee, aided by radiant heat, became normal by the eleventh day.

Acute pelvic inflammatory disease, causing moderate to severe pain, was seen in 6 of the 19 female patients. In 5 the pain was completely relieved within one to three days. The sixth patient was also immediately relieved, although she was intolerant of the drug and received only 1.5 Gm. within an eight hour period. Amelioration of the severe pain of acute adnexal involvement was consistent, striking and rapid.

*Toxic Manifestations.*—Even with the larger doses (6.0 Gm. a day) administered to the hospitalized group of patients, toxic manifestations were encountered less frequently and appeared to be less severe during treatment with sulfapyridine than with sulfanilamide. The patients receiving the smaller doses of sulfapyridine almost uniformly evidenced less toxic symptoms, and these of a milder character, than did those patients who were given the larger amounts. For this reason the tabulation of toxic manifestations (table 3) is divided into two groups.

Many of the toxic manifestations recorded were elicited only by recounting the possible symptoms. The probability of suggestion provoking an affirmative reply is not subject to a statistical analysis in this instance.

Most of the toxic symptoms noted in table 3 occurred for a day or two early in the course of treatment. In only 1 instance in the outpatient group was sulfapyridine intolerance pronounced enough to demand discontinuance of therapy.

It is not possible to offer data on the incidence of fever produced by sulfapyridine therapy in the outpatient group, but in the 210 hospitalized patients, in whom the temperature was recorded every four hours, only 1 patient developed a temperature of more than 37.6 C. (101.1 F.). In this man a temperature of 38.4 C. was noted on only a single day, the twelfth day of medication.

There was not any evidence which indicated that the production of toxic manifestations caused permanent ill effects.

*Correlation of Therapeutic Response, Clinical Course and Laboratory Studies.*—The results of the laboratory studies, outlined in an earlier statement, and their correlation with clinical experience may be summarized as follows:

1. The absorption of sulfapyridine was irregular and could be determined only by studies of the blood concentration.

2. The amount of acetylated sulfapyridine in the blood varied widely and offered no explanation for differences noted in toxic or treatment responses.

3. Constant blood levels of sulfapyridine in individuals on unchanged daily doses were not appreciably altered by fluid intakes up to 5,000 cc. a day. Therefore the initial restriction of fluid intake was abandoned.

4. Blood concentrations of 2 or 3 mg. per hundred cubic centimeters or less appeared sufficient for patients whose gonococcic infections were amenable to sulfapyridine therapy. The cure rate evidenced by the patients who had 5 to 14 mg. per hundred cubic centimeters of free sulfapyridine in the blood was approximately equal to the cure rate obtained in those in whom the blood level was below 5 mg. per hundred cubic centimeters.

5. In contradistinction to the results with sulfanilamide, there was not any clinical evidence of acidosis, nor was there a decrease in the carbon dioxide combining power of the plasma as determined in 27 cases studied.

6. There were not any instances of acute hemolytic anemia. There was a slight decrease in hemoglobin content in approximately one half of the patients under report. The remainder showed either no change or a slight increase in the content of hemoglobin while under treatment.

7. There were not any cases of granulocytopenia. Almost all of the patients had a slight elevation of the white cell count at the beginning of treatment, followed by a depression in the number of white cells to a level of 5,000 to 7,000 per cubic millimeter. Many of the patients showed temporary drops to counts between 4,000 and 5,000 cells per cubic millimeter. The cell count fell to 3,700 in only one instance but returned to a higher level on subsequent examinations without discontinuance of therapy. Differential cell counts showed a slight but uniform tendency toward monocytosis, reaching a maximum of 19 per cent in one case.

8. Hematuria was not found either by gross inspection or by the benzidine test. The dark color of some urines (negative by microscopic and benzidine tests for blood) suggested the presence of hematoporphyrin. The change in color of the urine did not interfere with routine treatment and disappeared after termination of the drug. Hematoporphyrinuria was not ascertained definitely because of a lack of suitable apparatus for precise spectroscopic examinations. There were not any symptoms suggestive of renal colic.

## COMMENT

From the practical point of view resulting from experience in treating 300 cases of gonococcic infection and the recorded results of twenty-two authors who treated 1,745 similar cases, it is evident that blood concentration studies have a limited clinical application in sulfapyridine therapy. It is also evident from the total lack of major toxic manifestations noted in this large collective group that blood counts, hemoglobin determinations and urinalyses may be dispensed with if the lack of laboratory facilities would otherwise curtail the use of the drug.

In the general management of the patients it was not found necessary to restrict any article of diet or to interdict any ordinary daily activity. The patients were cautioned concerning sexual excitement and the use of alcoholic beverages. However, a few of the outpatients continued to indulge in alcohol more or less freely during and subsequent to the administration of sulfapyridine; a lessening of the general cure rate in these patients was not noted.

As previously mentioned, the passage of sounds and prostatic massage became a routine procedure as soon as clinical and microscopic evidences of the disease were absent. This procedure was usually started on the fourth or fifth day after initiation of medication. Among the cases reported in this paper, in the treatment of which either sulfanilamide or sulfapyridine had been used and in which the demands of clinical cure and spread negativity had been satisfied, there was not a single instance of extension of the disease attributable to the practice. The passage of sounds and the prostatic massage on the fourth or fifth day of treatment may be regarded by some as therapeutic heresy, but if the precautions outlined are observed it is believed that these measures are not only harmless but actually enhance the cure rate by promoting early and adequate urethral drainage.

TABLE 3.—*Toxic Manifestations Resulting from Sulfapyridine Therapy*

| Toxic Manifestation | 200 Hospitalized Men — Sulfapyridine 6.0 Gm. 2 Days 3.0 Gm. 4-6 Days | | | 100 (10 Hospitalized Women) (9 Outpatient Women) (81 Outpatient Men) — Sulfapyridine 3.0 Gm. 1 Day 2.0 Gm. 6-9 Days | | |
|---|---|---|---|---|---|---|
| | Slight, % | Moderate, % | Severe, % | Slight, % | Moderate, % | Severe, % |
| Nausea | 27.0 | 25.5 | 4.5 | 28.0 | 4.0 | 1.0 |
| Vomiting | 13.0 | 4.0 | 2.0 | 7.0 | 3.0 | ... |
| Headache | 34.5 | 20.5 | 1.5 | 32.0 | 5.0 | 3.0 |
| Vertigo | 29.0 | 7.5 | ... | 19.0 | 1.0 | ... |
| Weakness | 4.5 | 13.5 | ... | 6.0 | 2.0 | ... |
| Anorexia | 16.5 | 7.0 | ... | 11.0 | 4.0 | ... |
| Insomnia | 11.5 | 4.5 | ... | 7.0 | 4.0 | ... |
| Dermatitis | 7.5 | 2.0 | ... | 5.0 | 1.0 | ... |
| Cyanosis | 2.5 | 1.0 | ... | 3.0 | ... | ... |
| Nervousness | ... | 0.5 | ... | 3.0 | ... | ... |
| Chilliness | ... | 0.5 | ... | ... | ... | ... |
| Backache | 1.5 | 1.0 | ... | 4.0 | ... | ... |
| Palpitation | ... | 0.5 | ... | 2.0 | ... | ... |
| Pruritus | ... | ... | ... | 1.0 | ... | ... |
| No toxic effect | 10% of patients | | | 39% of patients | | |

A few patients who failed on a first course of sulfapyridine and were therefore listed as failures obtained apparent cures following two or three weeks of rest or local therapy and a subsequent exhibition of the drug. A cure was effected in approximately two thirds of the group. These were, however, not included in the statistical analysis because (1) a second course of sulfapyridine was given in only a portion of the failures and (2) in the series under report primary interest has been to determine the ability of sulfapyridine to produce a successful outcome as a result of one course of administration. For the latter reason investigations have not been conducted concerning the advisability of concomitant local treatment. The literature reviewed suggested that a combination of local treatment with the oral administration of sulfapyridine generally added little if anything to the basic cure rate.

It has been previously mentioned that in persons failing to be cured of their gonococcic infections by sulfapyridine there was ample clinical evidence of the presence of the infection within six days of the discontinuance of medication. In discussing this point Herrold [4] also found that, "when cure was not effected

4. Herrold, R. D.: Comparative Efficacy of Sulfanilamide and Sulfapyridine in the Treatment of Gonococcal Infection, the Gonococcus and Gonococcal Infection, New York, Science Press, 1939, p. 140.

by one course of sulfapyridine, clinical exacerbation usually followed three to six days after the discontinuance of the drug."

The lack of a subclinical state is an important finding and is in contradistinction to our experience in the use of sulfanilamide, wherein a proportion of the failures were recorded as having asymptomatic infections which were elicited only by the finding of gonococci in cultures of urethral and/or prostatic secretions. Consequently when sulfapyridine is employed the absence of a subclinical, asymptomatic carrier state appears to minimize the necessity of prolonged observation and cultural studies as tests of cure.

Although the optimum time for administering sulfapyridine has not been definitely demonstrated, it appears from the results of the series under report and from the recorded data of many other investigators that sulfapyridine is as efficacious in very early acute cases as in infections of longer duration. The use of sulfapyridine in very early cases would appear, therefore, to aid materially in lessening the period of infectiousness without introducing a deleterious effect on the gross cure rate.

Both large and small dosages of sulfapyridine having been experimented with and the cure rates and the incidence and degree of toxic manifestations from each having been compared, it has become evident that the smaller doses, as prescribed for the outpatient group, are equally efficacious and considerably less toxic. It is also evident that the administration of sulfapyridine need occupy only the waking hours and need not be continued beyond seven to ten days. This means that the members of outpatient groups are able to continue their normal life with the obvious exceptions of indulgence in alcohol and sexual activity.

At the present time sulfapyridine appears to be the type of drug which can be applied on a broad basis to the control of gonococcic infections.

### SUMMARY AND CONCLUSIONS

1. There are obvious objections to the general use of sulfanilamide as an agent in the treatment of gonococcic infection.

2. Sulfapyridine was used in 300 cases of gonococcic infection. The cure rate approximated 85 per cent for patients who had not received previous chemotherapy and 70 per cent for those who had failed to benefit by earlier sulfanilamide treatment.

3. Subclinical carrier states were not encountered among patients treated with sulfapyridine.

4. The larger dosages (6 Gm. a day) were not more efficacious than the smaller ones (2 Gm. a day).

5. Toxic responses were encountered less frequently and in milder degrees in patients receiving the smaller doses.

6. Toxic manifestations were not serious and were significantly less than with sulfanilamide.

7. Prolonged administration is not indicated. Sulfapyridine therapy should be limited to a span of ten days or less.

8. Sound clinical judgment alone may serve as a practical guide for the use of sulfapyridine in the treatment of gonococcic infection, if the lack of laboratory facilities would otherwise curtail the use of the drug.

9. Sulfapyridine therapy appears applicable to the comprehensive treatment needs of the disease.

## DIFFUSION OF SULFONAMIDE COMPOUNDS INTO THE HUMAN PERICARDIUM

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With the introduction of methods for the estimation of sulfonamide compounds in blood and tissue, it was soon found that these compounds passed readily into most body tissue and fluids.[1] Observations have been made on saliva, milk, pleural fluid, spinal fluid, skin and sweat, bile, pancreatic juice, synovial fluid, placental blood and urine. With the exception of urine and spinal fluid, observations have not been extensive and there is still considerable information lacking concerning the distribution pattern of the various sulfonamide compounds in the body.

Long and Bliss [2] state that in the case of sulfanilamide the level in most body fluids is from 10 to 25 per cent lower than in the blood. Sulfanilamide is apparently more diffusible than sulfapyridine or sulfathiazole.

Long and Finestone [3] observed that sulfapyridine passed over into the spinal fluid in from one half to three fourths of the concentration which exists in the blood. It was found in pleural fluids in concentrations of about 75 per cent of that which was present in the blood.

Spink and Hansen,[4] in their clinical studies with sulfathiazole, found that this compound does not readily pass into spinal fluid. A survey of the literature fails to reveal any reference to the diffusion of sulfonamide compounds into the pericardial sac.

Observations have been made which indicate that the pericardial sac may be a relatively impermeable membrane. Drinker and Field [5] found that rabbit serum and horse serum are absorbed very slowly from the pericardial sac. Graphite particles of bacterial dimensions are removed very slowly and then only after phagocytosis. They concluded that the lymphatics in the basal portion of the pericardium are the principal source of drainage for these particles.

Stewart and his associates state [6] that they were unable to find observations relating to absorption from the human pericardial cavity. In a patient suffering from a chronic recurrent pericardial effusion of unknown etiology they found that a dye of the molecular order of phenolsulfonphthalein entered the blood stream readily from the pericardial cavity. Larger molecules, however, such as those of vital red, were not absorbed to any appreciable extent, and the dye was present in fluid removed a month later. Both dyes when injected intravenously failed to appear in the pericardial fluid.

This evidence of relative impermeability of pericardial membrane suggested a study of the diffusibility of

From the University of Southern California School of Medicine and the Medical Service, Cedars of Lebanon Hospital.

1. Marshall, E. K., Jr.; Emerson, Kendall, and Cutting, W. C.: Para-Aminobenzenesulfonamide, J. A. M. A. **108:** 952 (March 20) 1937.
2. Long, P. H., and Bliss, Eleanor A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, Macmillan Company, 1939, p. 73.
3. Long, P. H., and Finestone, W. H.: Observations on the Absorption and Excretion of Sulfapyridine, Proc. Soc. Exper. Biol. & Med. **39:** 486 (Dec.) 1938.
4. Spink, W. W., and Hansen, A. E.: Sulfathiazole, J. A. M. A. **115:** 840 (Sept. 7) 1940.
5. Drinker, C. K., and Field, M. E.: Absorption from the Pericardial Cavity, J. Exper. Med. **53:** 14 (Jan.) 1931.
6. Stewart, H. J.; Crane, N. F., and Dietrick, J. E.: Absorption from the Pericardial Cavity of Man, Am. Heart J. **16:** 198 (Aug.) 1938.

sulfonamide compounds into the pericardial sac. Two patients with chronic pericardial effusion were available for this study:

## REPORT OF CASES

CASE 1.—H. O., a white man aged 52, was first admitted to the medical service on Nov. 20, 1939. In May and June of 1939 he suffered several episodes of pain in the anterior part of the chest, radiating to the axillas. In October 1939 he noticed increasing dyspnea on exertion. At this time it was observed that his voice became high pitched and hoarse. Four weeks before admission he developed a dry, high-pitched cough, which persisted.

On admission, the physical examination revealed the following: The heart did not appear enlarged; the heart sounds were of poor quality but regular. The blood pressure was 102 systolic and 76 diastolic. Examination of the larynx showed a left recurrent laryngeal paralysis. The laboratory examination did not reveal anything significant. A six foot film of the heart showed the heart moderately increased in transverse diameter. An electrocardiogram showed low voltage with depressed T in all leads. The spinal fluid was negative; the venous pressure was 6 cm. of water. Circulation time studies were as follows: ether time 7 seconds, decholin circulation time 27 seconds.

The patient was discharged on December 30 with a diagnosis of myocardial deficiency, probably secondary to coronary disease.

He was readmitted on April 20, 1940. There had been increasing dyspnea on exertion since the discharge from the hospital. At this time there was definite evidence of increase in heart size, and signs of increasing congestive failure. The abdomen showed some distention and there was definite enlargement of the liver. On May 5, 1940, studies of circulation time showed the following: ether time 25 seconds, decholin circulation time 35 seconds. The venous pressure was 20 cm. of water. At this time a diagnosis of pericardial effusion was suspected, and on May 11, 1940, a pericardial puncture was done and 450 cc. of yellow fluid removed. This was followed by some improvement.

On July 16 another pericardial puncture was carried out and 600 cc. of thin, bloody fluid was removed and 400 cc. of air injected. On July 18, a chest film showed a typical hydropneumopericardium. On July 29 sodium sulfapyridine 3 Gm. dissolved in 30 cc. of distilled water was injected intravenously. One hour later a pericardial puncture was carried out; 600 cc. of bloody fluid was removed and 300 cc. of air injected. Estimation was made for free sulfapyridine in both the blood and the pericardial fluid at one hour and also at ninety minutes after administration of the drug. The results are summarized in the accompanying table. The pericardial fluid contained 4 Gm. of protein per hundred cubic centimeters.

A chest film taken two days later again showed the characteristic picture of a hydropneumopericardium. A loud friction rub could be heard following pericardial puncture. The patient developed increasing heart failure and died on Aug. 15, 1940.

An autopsy was done by Dr. L. J. Tragerman, and the anatomic diagnoses were:

1. Pericarditis, subacute, with effusion, etiology undetermined.
2. Pulmonary thrombosis.
3. Pulmonary atherosclerosis.
4. Chronic passive hyperemia of parenchymatous organs.

CASE 2.—J. H., a boy aged 17 years, admitted to the hospital on July 18, 1940, had entered the hospital on many occasions since 1938. He had suffered from bronchial asthma since 2½ years of age. During his first admission a muscle biopsy revealed the characteristic lesion of periarteritis nodosa. He also developed a pericardial effusion while in the hospital, and a paracentesis revealed fluid containing cells all of which were eosinophils. Since 1938 there had been repeated hospital admissions for severe status asthmaticus, but on three occasions he had entered the hospital with signs of cardiac decompensation and evidence of a pericardial effusion. On his last admission he showed definite dyspnea and orthopnea, distention of the jugular veins (venous pressure 22 cm. of water) enlargement of the liver and edema of the ankles. There was a rapid increase in the cardiac dulness and heart size by roentgen examination. Paracentesis of the pericardium was indicated, and sulfathiazole was administered in order to study the diffusibility of the drug into the pericardium. The drug was given in the following dosage: on August 16, 2 Gm. in divided doses; on August 17, 3 Gm.; on August 18 and 19, 4 Gm.; on August 20, 6 Gm., and on the morning of August 21, 3 Gm. was administered in one dose.

The blood level for sulfathiazole at 10:30 a. m. August 21 was 4.8 mg. At 11:30 a. m. 550 cc. of turbid pericardial fluid was removed and 250 cc. of air injected. The sulfathiazole level of the pericardial fluid was 4.7 mg. The specific gravity of the pericardial fluid was 1.011, the protein content 3 Gm. per hundred cubic centimeters.

After approximately a week there was evidence of reaccumulation of fluid in the pericardium, and the patient was prepared for another pericardial paracentesis. On August 29 he received 1.5 Gm. of sulfanilamide, and on August 31 and September 1 received 3 Gm. daily of the drug. On September 2 the blood sulfanilamide level was 4.0 mg. At this time 400 cc. of pericardial fluid was removed. The sulfanilamide level of the pericardial fluid was 4 mg.

*Blood and Pericardial Fluid Levels of Sulfonamide Compounds in Milligrams of Free Compound per Hundred Cubic Centimeters*

| Patient | Compound | Blood Level | Pericardial Fluid Level |
|---|---|---|---|
| H. O. ..... | Sulfapyridine, sodium salt 3 Gm. by vein | 6 mg., 60 minutes after injection<br>6 mg., 90 minutes after injection | 1.9 mg., 60 minutes after injection<br>2.3 mg., 90 minutes after injection |
| J. H. ..... | Sulfathiazole 22 Gm. by mouth in 5 days | 4.8 mg. | 4.7 mg. |
| J. H. ..... | Sulfanilamide 10.5 Gm. by mouth in 4 days | 4.0 mg. | 4.0 mg. |

A comparative study was also made of the blood protein and the pericardial fluid protein. The total blood protein was 7.3 Gm., the pericardial fluid protein 1.3 Gm. per hundred cubic centimeters.

## COMMENT

These observations indicate that there is a free diffusion of sulfanilamide and sulfathiazole into the pericardial sac. A possible explanation for the lower levels of sulfapyridine in the pericardial fluid is that a sufficient time had not elapsed for a more complete removal of the drug from the blood. This, however, seems unlikely, as the observations of Marshall and Long[7] indicate that after an intravenous injection of sodium sulfapyridine the distribution of the drug between the blood and the body tissues is complete or nearly complete from five to ten minutes after the injection is completed.

The practical implication of these observations is quite obvious. It is important in administering these drugs to be certain that they reach the affected tissues in concentrations which have a therapeutic effect.

Since infection of the pericardium may be due to organisms such as the pneumococcus, streptococcus and staphylococcus, which are susceptible to the sulfonamide compounds, these drugs should be indicated in pericardial inflammations due to these organisms.

658 South Bonnie Brae Street.

7. Marshall, E. K., Jr., and Long, P. H.: The Intravenous Use of Sodium Sulfapyridine, J. A. M. A. **112**: 1671 (April 29) 1939.

# STUDIES ON THE PHARMACOLOGY OF SULFAPYRIDINE AND SULFATHIAZOLE

## THE ABSORPTION OF THE FREE ACID, THE SODIUM SALT AND THE GLUCOSIDE FROM THE ALIMENTARY TRACT

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It is well known that the absorption of certain sulfanilamide derivatives, such as sulfapyridine and sulfanilyl-sulfanilamide, from the gastrointestinal tract is extremely erratic, so that marked variations in blood concentrations occur in different individuals after unit dosages. Some time ago Marshall and his co-workers [1] took issue with the oral L. $D._{50}$ for sulfapyridine in mice as reported by Wien.[2] They contended that the latter author used the water insoluble free acid for determining toxicity levels, which is absorbed in so irregular a manner as to render the results unreliable. Marshall showed that when the sodium salt was administered instead of the free acid a definite relationship could be demonstrated between the dosage and the blood level; the L. $D._{50}$ of sulfapyridine administered as the water soluble sodium salt was approximately one-eighth that of the free acid as obtained by Wien.

The freely soluble sulfapyridine sodium is rapidly converted to the insoluble free acid when placed in an acid medium or when the high alkalinity of the solution is materially reduced. It would be reasonable to expect, therefore, that in the stomach of an individual with a normal or high hydrochloric acid level the sodium salt would rapidly be converted to the free acid. Any material which would pass unchanged out of the stomach into the small intestine would be absorbed as the sodium salt. The absorption of such a salt from the gastrointestinal tract should therefore be primarily a function of the quantity of free acid in the stomach and the emptying time of the stomach.

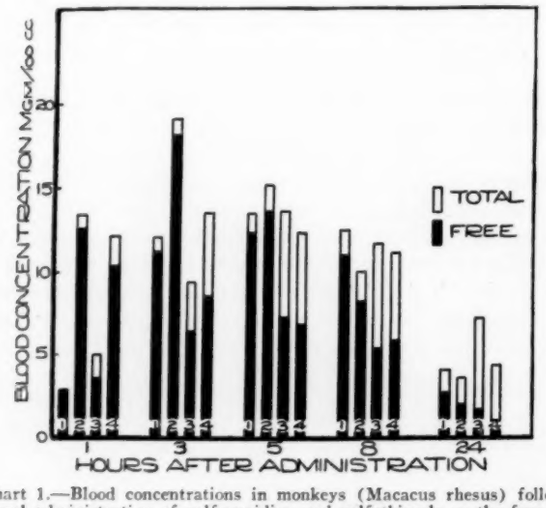


Chart 1.—Blood concentrations in monkeys (Macacus rhesus) following the oral administration of sulfapyridine and sulfathiazole as the free acids and sodium salts (1.0 Gm. per kilogram). 1, sulfathiazole (acid). 2, sulfathiazole (sodium salt). 3, sulfapyridine (acid). 4, sulfapyridine (sodium salt).

Our experiences in determining the oral toxicity of sulfathiazole and certain related compounds have closely paralleled those of Marshall with sulfapyridine in that we found it impossible to obtain clear cut, reproducible values after the oral administration of the insoluble free acids, whereas such results were obtainable after the oral administration of the sodium salts. These data have already been presented.[3]

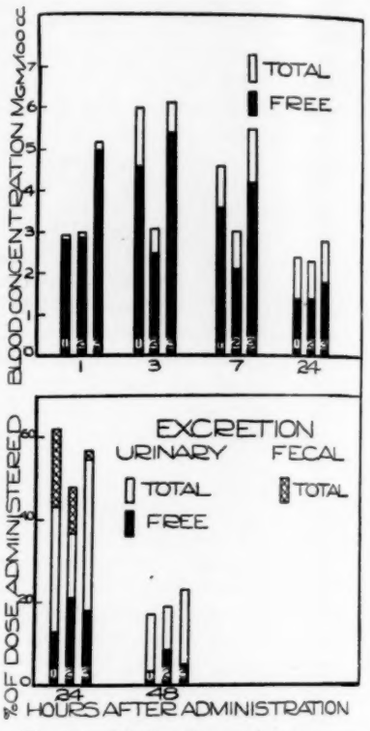


Chart 2.—Blood, urine anad fecal concentrations of sulfapyridine following the oral administration of a single dose (4 Gm.) as the free acid, the sodium salt and the glucoside, to men. Form of administration: 1, acid. 2, glucoside. 3, sodium salt.

It is believed that the differences in rate of absorption of the various forms of these chemotherapeutic agents which we observed was of sufficient practical importance to warrant careful examination. In a series of experiments both the sodium salts and the free acids of the drugs in question were administered to the same experimental individuals and their absorption and excretion were determined by the concentration of the drug in the blood, urine and feces. In addition, certain of our experimental groups were also used for a similar study on the glucose derivatives of these compounds, and on the effect of the simultaneous administration of antacids.

The first series consisted of a group of nine normal adult monkeys (Macacus rhesus) of both sexes. The animals were kept on a normal mixed diet, and in all instances the drugs were administered by stomach tube prior to the morning meal, a uniform dose of 1 Gm. per kilogram of the compounds being used throughout the series. In the case of the free acids of sulfapyridine and sulfathiazole, a very finely ground 100 mesh powder was suspended in a sufficient quantity of milk to make 10 per cent suspensions. A high speed rotary blender was used to make uniform suspensions. The sodium salts were administered as 10 per cent aqueous solutions. Blood concentrations were determined by means of a slight modification of Marshall's method. The results given in chart 1 were obtained. The mean values, noted in milligrams per hundred cubic centimeters, are shown diagrammatically. A study of these results brings out the following points:

1. The aqueous solutions of the sodium salts of sulfathiazole and sulfapyridine are absorbed from the gastrointestinal tract

From the Research Laboratories of the Winthrop Chemical Company, Inc.

1. Marshall, E. K., Jr.; Bratton, A. C., and Litchfield, J. R., Jr.: The Toxicity and Absorption of 2-Sulfanilamidopyridine and Its Soluble Sodium Salt, Science **88**: 597, 1938.

2. Wien, R.: The Toxicity of 2-Sulfanilamidopyridine, Quart. J. Pharm. & Pharmacol. **11**: 217, 1938.

3. Report on the Pharmacology and Toxicology of Sulfathiazole Submitted to the Bureau of Food and Drugs, U. S. Department of Agriculture, by the Winthrop Chemical Company.

more rapidly than are the suspensions of their respective free acids.

2. The sodium salt of sulfapyridine behaves in the same manner as does the sodium salt of sulfathiazole.

3. The peak concentration following the administration of a given dose of the sodium salt of either compound is considerably higher than the peak concentration after the same quantity of the free acid. The differences are maximal at the expiration of one hour and are demonstrable in decreasing degree up to the seventh hour but largely or completely disappear thereafter.

4. In the case of the monkey (Macacus rhesus), a much larger proportion of sulfapyridine is conjugated than of sulfathiazole. This is true regardless of whether the drug is administered as the free acid or the sodium salt.

Because of the two anomalous results which were observed in this series, the detailed protocol of the experiment is given in table 1.

the sodium salt or the glucoside was administered, for example, the dose was adjusted to contain 4 Gm. of the free acid. In some instances, sulfathiazole was administered as the free acid in capsule form followed immediately by aqueous suspensions of sodium bicarbonate or magnesium oxide.

The results of this experiment are shown in detail in table 2, while charts 2 and 3 give the mean values obtained.

With doses of this order the absorption of sulfapyridine is somewhat greater than the absorption of sulfathiazole. The blood concentrations of the free or uncombined (and therapeutically effective) form of the two drugs are the same for the two compounds. The total blood concentration of sulfapyridine, however, is considerably higher than the total blood concentration of sulfathiazole because of the fact that the degree of

TABLE 1.—*Blood Concentrations in Milligrams per Hundred Cubic Centimeters in a Series of Monkeys Following the Oral Administration of Sulfapyridine and Sulfathiazole as the Free and the Sodium Salt*

| | | Blood Concentration, Mg. per 100 Cc. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 Hour | | 3 Hours | | 5 Hours | | 8 Hours | | 24 Hours | |
| Drug | Monkey No. | Free | Total | Free | Total | Free | Total | Free | Total | Free | Total |
| Sulfathiazole | 28 | 3.9 | 3.9 | 16.0 | 17.6 | 12.8 | 13.7 | 12.5 | 14.6 | 1.2 | 1.6 |
| Sulfapyridine | | ... | ... | 7.3 | 10.9 | 6.7 | 14.4 | 3.7 | 8.8 | 2.9 | 8.9 |
| Sodium sulfathiazole | | 21.0 | 21.9 | 33.6 | 35.2 | 23.2 | 25.2 | 13.8 | 15.0 | 0.9 | 1.3 |
| Sodium sulfapyridine | | 12.7 | 15.6 | 8.4 | 15.2 | 5.6 | 13.7 | 4.3 | 10.9 | 0.5 | 1.3 |
| Sulfathiazole | 29 | 1.0 | 1.0 | 12.2 | 12.0 | 13.9 | 15.6 | 15.0 | 16.7 | 2.7 | 3.5 |
| Sulfapyridine | | 1.3 | 1.9 | 4.6 | 6.0 | 6.0 | 11.7 | 4.6 | 10.7 | 1.1 | 8.5 |
| Sodium sulfathiazole | | 13.9 | 14.5 | 14.0 | 16.3 | 11.9 | 12.5 | 5.1 | 5.7 | 0.6 | 0.7 |
| Sodium sulfapyridine | | 8.9 | 10.8 | 6.7 | 13.3 | 4.7 | 11.9 | 3.5 | 10.6 | 0.7 | 2.1 |
| Sulfathiazole | 30 | 3.1 | 3.1 | 11.7 | 13.7 | 13.0 | 14.9 | 9.3 | 10.7 | 1.1 | 1.1 |
| Sulfapyridine | | 5.9 | 7.6 | 7.7 | 11.5 | 7.1 | 14.4 | 4.3 | 10.6 | 0.8 | 4.8 |
| Sodium sulfathiazole | | 11.2 | 11.6 | 21.2 | 22.2 | 14.1 | 14.7 | 6.5 | 7.6 | 0.9 | 1.2 |
| Sodium sulfapyridine | | 7.4 | 10.1 | 4.7 | 10.5 | 3.4 | 9.5 | 2.3 | 8.2 | 0.5 | 1.7 |
| Sulfathiazole | 31 | 2.6 | 3.0 | 11.1 | 12.6 | 13.8 | 15.6 | 8.2 | 10.7 | 5.1 | 15.3 |
| Sulfapyridine | | 3.2 | 6.2 | 4.3 | 9.2 | 7.4 | 20.1 | 6.8 | 22.8 | ... | .... |
| Sodium sulfathiazole | | 13.4 | 17.0 | 13.2 | 14.0 | 17.3 | 25.5 | 12.4 | 24.0 | 6.8 | 19.4 |
| Sodium sulfapyridine | | .... | .... | .... | .... | .... | .... | .... | .... | ... | .... |
| Sulfathiazole | 32 | 2.8 | 2.8 | 8.9 | 9.2 | 9.7 | 9.7 | 12.5 | 13.2 | 1.2 | 1.6 |
| Sulfapyridine | | 2.5 | 3.1 | 6.8 | 8.8 | 9.6 | 13.5 | 8.7 | 12.5 | 1.4 | 8.7 |
| Sodium sulfathiazole | | 17.5 | 17.8 | 19.8 | 21.6 | 15.9 | 16.4 | 5.7 | 6.3 | 2.4 | 2.4 |
| Sodium sulfapyridine | | 15.9 | 17.3 | 14.7 | 22.7 | 11.9 | 18.3 | 10.9 | 17.5 | 2.3 | 12.8 |
| Sulfathiazole | 33 | 4.8 | 4.8 | 12.5 | 13.3 | 16.3 | 17.7 | 9.7 | 11.1 | 1.3 | 1.7 |
| Sulfapyridine | | 3.7 | 5.4 | 4.5 | 7.3 | 3.8 | 9.7 | 3.2 | 7.8 | 1.0 | 1.2 |
| Sodium sulfathiazole | | 6.6 | 6.6 | 3.4 | 4.0 | 3.8 | 4.2 | 2.8 | 2.8 | 0.8 | 1.0 |
| Sodium sulfapyridine | | 8.0 | 10.5 | 4.3 | 9.0 | 2.9 | 7.8 | 1.6 | 4.7 | 0.5 | 0.9 |
| Sulfathiazole | 34 | 3.8 | 3.8 | 10.3 | 10.3 | 12.5 | 13.9 | 8.2 | 9.0 | 5.3 | 6.4 |
| Sulfapyridine | | 3.4 | 3.7 | 5.6 | 6.5 | 5.6 | 8.3 | 5.7 | 9.5 | 2.3 | 7.9 |
| Sodium sulfathiazole | | 10.0 | 10.0 | 20.4 | 20.4 | 13.0 | 13.0 | 7.9 | 8.8 | 3.2 | 3.4 |
| Sodium sulfapyridine | | 15.7 | 16.6 | 9.9 | 13.2 | 9.1 | 13.3 | 8.3 | 12.7 | 1.0 | 3.5 |
| Sulfathiazole | 35 | 2.4 | 2.4 | 12.2 | 12.9 | 11.8 | 12.4 | 13.2 | 14.7 | 1.7 | 1.7 |
| Sulfapyridine | | 5.4 | 6.6 | 10.3 | 13.3 | 10.0 | 15.4 | 5.9 | 10.3 | 1.7 | 4.9 |
| Sodium sulfathiazole | | 3.2 | 3.8 | 16.3 | 16.5 | 9.9 | 9.9 | 5.5 | 5.8 | 1.2 | 1.6 |
| Sodium sulfapyridine | | 11.1 | 12.4 | 15.7 | 20.5 | 12.9 | 18.3 | 10.3 | 15.2 | 0.9 | 2.0 |
| Sulfathiazole | 36 | 1.2 | 1.2 | 6.3 | 7.0 | 7.6 | 8.5 | 10.4 | 12.0 | 3.6 | 3.7 |
| Sulfapyridine | | 3.5 | 4.4 | 7.3 | 10.3 | 8.9 | 15.3 | 5.7 | 11.9 | 1.7 | 12.0 |
| Sodium sulfathiazole | | 16.5 | 17.1 | 21.7 | 22.9 | 14.9 | 15.8 | 13.5 | 14.2 | 1.1 | 1.2 |
| Sodium sulfapyridine | | 2.5 | 3.8 | 3.7 | 6.9 | 4.4 | 6.5 | 4.8 | 8.8 | 1.5 | 9.6 |

Monkey 33 showed a generally lower blood level after the administration of the sodium salt of sulfathiazole than after the administration of the same quantity of the free acid. This reversal was evident also following the administration of sulfapyridine and its sodium salt. Monkey 36 absorbed sulfathiazole and its sodium salt in the normal manner; i. e., the blood level was considerably higher after the administration of the sodium salt than after the administration of the free acid. However, this relationship was reversed when sulfapyridine and its sodium salt were administered, for the administration of the free acid gave rise to a generally higher blood concentration than was observed after the administration of the sodium salt. These anomalies will be discussed later.

A similar experiment was carried out on a group of six normal men. A fixed dose of 4 Gm. of the drug was administered to all individuals regardless of the form of the drug or the size of the subject. When

conjugation of sulfapyridine is much greater than that of sulfathiazole.

This difference in the degree and rate of conjugation of the two compounds also manifests itself in the urinary excretion of the two drugs. Approximately 40 per cent of the total amount of each drug administered is excreted in the urine in the first twenty-four hours; in the case of sulfapyridine 30 per cent of the drug excreted is in the free form, while the remainder has been acetylated; in the case of sulfathiazole 77 per cent of the excreted drug is in the free form. The relative degree of conjugation which occurs in animals and in man is the same regardless of whether the drug is administered in the form of the free acid or of the soluble sodium salt.

The absorption of either sulfapyridine or sulfathiazole from the gastrointestinal tract is more rapid, and a persistently higher blood level is maintained throughout the entire period of observation after the administration of

the sodium salt as compared with the poorly soluble free acids. Another point observed in the monkey series is also shown here. The total blood concentration after the administration of the sodium salt of sulfapyridine is somewhat higher than that which is observed following the administration of the sodium salt of sulfathiazole. This difference is due entirely to the greater proportion of conjugated sulfapyridine present: the concentrations of the free form of the drugs are the same.

In addition to the higher blood concentrations following the administration of the drugs as the sodium salts, the increased absorption rate manifests itself by an increase in the urinary output of the drugs. Here again the difference in the rate of conjugation of the pyridine derivative and the thiazole derivative is obvious.

In the human series one anomalous result was observed similar to that recorded in the series of monkeys: Subject E. O. showed a higher blood level following the administration of sulfapyridine as the free acid than he did after the administration of the same dose of the drug in the form of the sodium salt. As we mentioned before, the absorption of such a salt from the gastrointestinal tract is a function of the rapidity with which the drug leaves the stomach and the amount of acid in the stomach. An attempt was made to correlate the degree of gastric acidity with the absorption of the sodium salts in the series of monkeys. On three occasions the response of the fasting animals to the subcutaneous injections of histamine was examined. The results, however, were so variable as to afford little help in elucidating the problem. This variation was undoubtedly due to the excitement associated with restraining the animals and passing the stomach tube. The emptying time of the stomach, however, gave better data. A barium sulfate test meal [4] was administered by stomach tube, and the animals were examined under the fluoroscope at periodic intervals thereafter. Two animals in the series had a marked increase in the emptying time of the stomach associated with spasm of the pylorus. These animals also showed the anomalous result in the absorption of the free acids and the sodium salts. It would be reasonable to assume that a similar mechanism was involved in the reversal of the absorption rate seen in subject E. O., who likewise showed a retention and complained of persistent nausea, regurgitation of gastric contents and heartburn after the administration of the sodium salt.

TABLE 2.—*Blood Concentrations in Milligrams per Hundred Cubic Centimeters; Urinary and Fecal Excretions as Percentage of Dose Administered in Man Following Oral Administration of 4 Gm.*

| | | Blood Concentration, Mg. per 100 Cc. | | | | | | | | | | Urinary Excretion as Percentage of Dose Administered | | | | Fecal Excretion as Percentage of Dose Administered | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 Hour | | 3 Hours | | 7 Hours | | 24 Hours | | 48 Hours | | 24 Hours | | 48 Hours | | | | |
| Subject | Drug | Free | Total | Free | Total | Free | Total | Free | Total | Free | Total | Free | Total | Free | Total | 24 Hrs. | 48 Hrs. | Notes |
| E. O. | Sulfapyridine | 3.3 | 4.0 | 4.7 | 6.2 | 3.4 | 5.2 | 1.2 | 2.4 | ... | ... | 17.0 | 62.0 | 2.5 | 13.0 | 15.5 | ... | Nil |
| | Sodium sulfapyridine | 3.3 | 3.3 | 4.8 | 5.3 | 3.6 | 4.6 | 1.4 | 2.2 | Trace | | 18.0 | 61.0 | 3.5 | 19.0 | 5.0 | 3.5 | Nausea; dizzy |
| | Sulfapyridine glucoside | 2.1 | 2.1 | 2.1 | 2.9 | 1.9 | 3.0 | 0.9 | 1.8 | ... | ... | 14.0 | 45.0 | 3.5 | 19.0 | 12.0 | ... | Nil |
| | Sulfathiazole plus sodium bicarbonate | 3.9 | 3.9 | 6.7 | 6.7 | 3.3 | 3.7 | 1.0 | 1.0 | ... | ... | 58.0 | 78.0 | 4.5 | 8.0 | .... | ... | Nil |
| J. O'C. | Sulfapyridine | 2.2 | 2.4 | 5.0 | 5.7 | 4.7 | 5.7 | 1.2 | 2.1 | ... | ... | 11.0 | 35.0 | 3.2 | 15.0 | 17.5 | ... | Nil |
| | Sodium sulfapyridine | 6.1 | 6.2 | 6.5 | 7.6 | 4.8 | 7.0 | 1.7 | 3.2 | 0.0 | 0.4 | 16.7 | 53.5 | 5.0 | 24.5 | 0.6 | 1.3 | "Upset stomach"; no nausea |
| | Sulfapyridine glucoside | 2.7 | 2.8 | 1.8 | 2.3 | 2.2 | 3.2 | 2.2 | 3.9 | 1.5 | 3.1 | 11.0 | 32.7 | 8.0 | 35.5 | 5.5 | ... | Nil |
| | Sulfathiazole plus sodium bicarbonate | 3.7 | 3.7 | 3.8 | 4.1 | 2.1 | 2.3 | 1.3 | 1.3 | ... | ... | 27.2 | 36.7 | 5.2 | 8.0 | ... | ... | Nil |
| H. K. | Sulfapyridine | 2.4 | 2.4 | 4.1 | 5.0 | 2.7 | 3.4 | 1.9 | 2.6 | ... | ... | 10.5 | 34.0 | 5.5 | 22.7 | 25.7 | ... | Nil |
| | Sodium sulfapyridine | 5.6 | 6.2 | 5.0 | 5.4 | 4.2 | 4.9 | 2.0 | 2.9 | 0.0 | 0.3 | 19.2 | 54.2 | 6.0 | 27.5 | 1.3 | 1.8 | Slight nausea; dizzy |
| | Sulfapyridine glucoside | 3.8 | 4.0 | 3.5 | 4.0 | 2.3 | 2.7 | 0.9 | 1.2 | ... | ... | 33.7 | 44.7 | 13.7 | 20.0 | 13.0 | ... | Nil |
| | Sulfathiazole plus sodium bicarbonate | 4.2 | 4.2 | 9.0 | 9.5 | 3.6 | 3.6 | 1.2 | 1.2 | ... | ... | 58.5 | 75.5 | 5.5 | 8.2 | .... | ... | "Blood to head" |
| M. F. | Sulfathiazole | 2.4 | 2.4 | 4.0 | 4.4 | 3.8 | 4.2 | 1.0 | 1.1 | ... | ... | 24.7 | 37.2 | 3.2 | 5.2 | 11.5 | ... | Nil |
| | Sodium sulfathiazole | 7.3 | 7.3 | 5.8 | 5.8 | 3.3 | 3.4 | 0.9 | 0.9 | ... | ... | 44.7 | 60.5 | 2.7 | 7.0 | 6.7 | 0.5 | Nausea; "gas" |
| | Sulfathiazole glucoside | 3.6 | 3.6 | 3.4 | 3.5 | 2.3 | 2.5 | 1.1 | 1.1 | ... | ... | 33.0 | 47.5 | 6.0 | 9.7 | 12.5 | ... | Nil |
| W. K. | Sulfathiazole plus magnesium oxide | 6.7 | 6.7 | 7.4 | 7.5 | 4.8 | 4.8 | 1.8 | 1.8 | ... | ... | 18.5 | 24.5 | 6.5 | 9.2 | .... | ... | Diarrhea; dizzy |
| D. S. | Sulfathiazole | 1.3 | 1.3 | 4.6 | 4.6 | 4.5 | 4.6 | 1.1 | 1.3 | ... | ... | 44.5 | 55.2 | 7.7 | 11.0 | 0.2 | ... | Slight cyanosis |
| | Sodium sulfathiazole | 4.6 | 4.6 | 6.9 | 6.9 | 4.7 | 5.2 | 1.2 | 1.2 | 0.0 | 0.0 | 60.2 | 72.0 | 6.2 | 9.2 | 0.5 | ... | Dizzy |
| | Sulfathiazole glucoside | 2.5 | 2.5 | 4.0 | 4.1 | 3.5 | 3.7 | 3.9 | 4.5 | 3.7 | ... | 24.2 | 35.7 | 16.2 | 29.5 | 0.1 | 1.1 | Nil |
| | Sulfathiazole plus magnesium oxide | 0.5 | 0.5 | 7.6 | 7.6 | 5.5 | 5.5 | 1.8 | 2.1 | ... | ... | 75.7 | 90.5 | 7.5 | 10.0 | ... | ... | Diarrhea |
| E. M. | Sulfathiazole | 2.1 | 2.1 | 4.4 | 4.5 | 2.3 | 2.4 | 0.6 | 0.8 | ... | ... | 20.7 | 26.0 | 5.7 | 8.0 | Trace | ... | Sluggish |
| | Sodium sulfathiazole | 4.7 | 4.7 | 7.3 | 7.3 | 3.8 | 4.0 | 0.9 | 0.9 | 0.0 | ... | 55.0 | 70.7 | 4.7 | 6.5 | 1.5 | 2.2 | Nausea; "gas" |
| | Sulfathiazole glucoside | 4.1 | 4.1 | 3.7 | 3.7 | 2.3 | 2.3 | 1.3 | 1.3 | ... | ... | 36.7 | 44.5 | 11.7 | 15.5 | 20.5 | ... | Nil |
| | Sulfathiazole plus magnesium oxide | 3.0 | 3.0 | 5.8 | 5.8 | 4.3 | 4.3 | 1.2 | 1.2 | ... | ... | 26.1 | 32.2 | 8.7 | 11.7 | .... | ... | Diarrhea |

The water soluble glucosides of these compounds, while susceptible to hydrolytic breakdown, are more stable to $p_H$ change than their respective sodium salts. We have observed the precipitation of the free acid at the point of contact during the injection by syringe of a 5 per cent solution of sodium sulfapyridine into a buffered Ringer-Locke solution at $p_H$ 7.4. When the glucoside is incubated for one hour at 37 C. in 0.3 per cent hydrochloric acid solution, only about 50 per cent of the drug will be reduced to the uncombined form. Thus, in a

TABLE 3.—*Uncombined Sulfapyridine and Sulfathiazole*

| Time of Incubation | Percentage of Drug in Uncombined Form | |
|---|---|---|
| | Sulfathiazole | Sulfapyridine |
| 0 minutes | 17.5 | 15.0 |
| 30 minutes | 53.9 | 59.5 |
| 60 minutes | 66.1 | 70.5 |
| 120 minutes | 68.6 | 71.2 |
| 240 minutes | 68.6 | 71.0 |

4. Bananas 400 Gm., milk 300 Gm., barium sulfate 200 Gm. and sodium bicarbonate 100 Gm.

simple experiment 10 cc. of a 10 per cent solution of the sulfapyridine glucoside was added to 50 cc. of 0.3 per cent hydrochloric acid solution and incubated at 37 C. Samples were removed at periodic intervals and analyzed for uncombined sulfapyridine. A similar system was set up with sulfathiazole glucoside.

In spite of apparently greater stability of the more soluble glucoside in the presence of acid, this compound is absorbed from the intestine considerably slower than the sodium salt and even slightly slower than the free acid. These results confirm the work of Finland, Taylor and their associates,[5] who were unable to show any significant difference in the absorption of sulfapyridine whether administered as the glucoside or the free acid.

Sodium bicarbonate is frequently administered in combination with sulfanilamide in order to improve the tolerance and to correct a tendency to acidosis. Acidosis rarely occurs after sulfapyridine or sulfathiazole therapy, and the absence of change in the alkali reserve

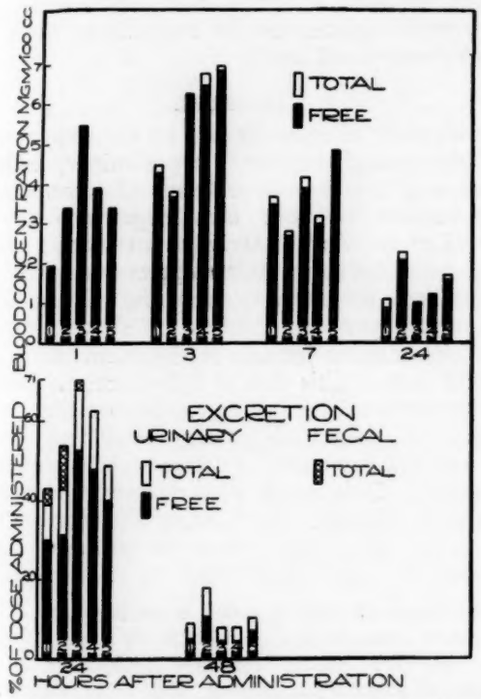


Chart 3.—Blood, urine and fecal concentrations of sulfathiazole following the oral administration of a single dose (4 Gm.) as the free acid, the sodium salt, the glucoside, the free acid in combination with sodium bicarbonate and the free acid in combination with magnesium oxide to men. Form of administration: 1, acid. 2, glucoside. 3, sodium salt. 4, acid + sodium bicarbonate. 5, acid + magnesium oxide.

after such medication suggests that supplementary medication with antacids is unnecessary. The alteration of the usual absorption curve of sulfanilamide derivatives when administered as the sodium salts suggested that the difference noted might be due in part to an altered emptying time and seemed worthy of examination, since such alterations may be induced by the administration of antacids. Sulfathiazole was administered as the free acid in capsules followed immediately by an aqueous suspension of sodium bicarbonate or magnesium oxide in doses of 4 Gm. and 3 Gm. respectively. The addition of the alkali caused a marked increase in the rate of absorption of the free acid, giving rise to a blood concentration approaching that resulting from the administration of the sodium salt. The addition of sodium bicarbonate gave rise to practically no untoward symptoms, but the addition of magnesium oxide caused diarrhea in every instance.

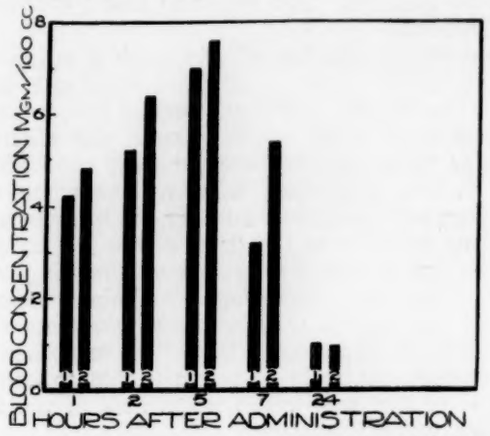


Chart 4.—Blood concentration of sulfathiazole in dogs following the oral administration of 148 mg. per kilogram of sulfathiazole as the free acid and as the glucoside: 1, sulfathiazole glucoside. 2, sulfathiazole acid.

In dogs and rats the administration of sulfathiazole in the form of the free acid and the glucoside gives essentially the same result as has been described for man. In both of these species the blood level following the administration of the glucoside more closely approaches that following the administration of the free acid than it does in man. These results are shown in charts 4 and 5.

## SUMMARY

1. The sodium salts of sulfapyridine and sulfathiazole are absorbed from the gastrointestinal tracts of man and monkey more rapidly than are their respective free acids.

2. The glucosides of sulfapyridine and sulfathiazole are absorbed from the gastrointestinal tract of man, dogs and rats less rapidly than are their respective free acids.

3. The simultaneous administration of alkali in the form of sodium bicarbonate or magnesium oxide with sulfathiazole hastens the absorption of this compound from the gastrointestinal tract of man.

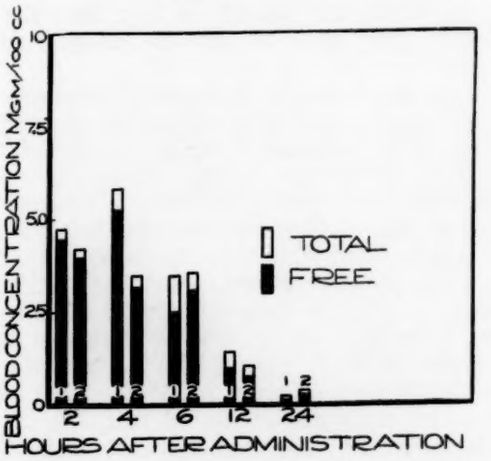


Chart 5.—Blood concentration of sulfathiazole in rats following the oral administration of a single dose (250 mg. per kilogram) of sulfathiazole as the free acid and as the glucoside: 1, sulfathiazole (acid). 2, sulfathiazole (glucoside).

5. Taylor, F. H. L.; Lowell, F. C.; Adams, M. A.; Spring, W. C., and Finland, Maxwell: A Comparative Study of the Blood Concentration and Urinary Excretion of Sulfapyridine and Sulfanilamide After Single Doses of Sulfapyridine and Related Compounds Administered by Various Routes, J. Clin. Investigation **19:** 201, 1940. Finland, Maxwell; Lowell, R. C.; Spring, W. C., and Taylor, F. H. L.: Intravenous Use of Sodium Sulfapyridine and Report of Clinical and Laboratory Observations on the Use of Glucose Sulfapyridine Solution, Ann. Int. Med. **13:** 1105, 1940.

4. In rate and degree, conjugation of sulfapyridine is higher than that of sulfathiazole in man and monkey.

5. Following the oral administration of equal doses, the blood concentration of unconjugated sulfapyridine is practically the same as that of unconjugated sulfathiazole. The total blood concentration of sulfapyridine, however, is higher than the total blood concentration of sulfathiazole.

Since the completion of this work a study on the absorption and excretion of the sodium salt of sulfapyridine in man has been published by Ratish, Davidson and Bullowa.[6] Our results support the observations made by these authors save for their conclusion that there is less acetylation following the administration of sodium sulfapyridine than after the administration of the same quantity of the drug as the free acid. The ratio of unconjugated drug to total drug is greater in the first few hours following the administration of the sodium salt than it is after the administration of the same dose of the free acid, but within seven hours after such dosage the ratio of unconjugated to conjugated drug is of the same order, regardless of the form in which it was administered.

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# THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

## PRESENT STATUS

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Until recently all forms of treatment of patients with subacute bacterial endocarditis were adjudged ineffective. Except for a rare spontaneous remission of the disease, the outcome has generally been accepted as fatal. The recent application of artificial hyperthermia and new chemotherapeutic agents to the treatment of bacterial infections fostered the hope that the outlook for recovery in subacute bacterial endocarditis might improve.

In 1933 one of us (W. B.) applied physically induced pyrexia without additional chemotherapy to a patient suffering from subacute bacterial endocarditis. At the time this patient was actively embolizing. Following the second fever treatment showers of numerous emboli caused an exitus. Postmortem examination showed the viscera to be filled with numerous fresh and old emboli.

In 1936 Krusen [1] experimented with artificial fever therapy in subacute bacterial endocarditis and abandoned it because of apparently increased danger of embolism. In 1937 Dry and Willius [2] treated 4 patients who had proved subacute bacterial endocarditis with therapeutic fever and concluded that, despite the fact that fever therapy enhanced cellular reactions and the defense processes of the host, Streptococcus viridans appeared to be able to resist the highest temperature to which it is safe to expose the human body. The results with gonococcic endocarditis were far more encouraging; however, the results of treatment of this form of endocarditis will not be included in this communication.

In 1938 Baehr and Bierman [3] successfully treated a patient with hyperpyrexia and sulfanilamide. Clubbing of the fingers disappeared within three weeks after the blood culture became sterile. In 1940 Krusen and Bennett [4] treated six patients with combined fever and sulfanilamide without success. The combined therapy appeared to have a definite although transient influence on the disease; either a definite decrease occurred in the number of bacterial colonies on culture of the blood following treatment, or the blood cultures became negative temporarily. Encouraged by White's [5] observation that the bactericidal properties of sulfanilamide were increased one hundredfold with a rise of temperature from 37 to 39 C., Solomon [6] proceeded to treat patients who had subacute bacterial endocarditis with artificial hyperpyrexia induced by the intravenous use of killed typhoid-paratyphoid bacilli.

### MATERIAL

The number of cases treated by the new methods is now large enough to permit a preliminary estimate of the value of the respective forms of treatment. Published reports and our own experience have been reviewed in an effort to arrive at a tentative conclusion as to which method of treatment at present offers the greatest hope for recovery from the disease. For this purpose only permanent cures are significant.

The presentation consists of 55 patients with subacute bacterial endocarditis due to Streptococcus viridans or nonhaemolyticus [7] treated at the Mount Sinai Hospital between the period of January 1939 and September 1940 and 232 cases collected from other sources (total, 287 cases). Only cases that received adequate treatment were selected. There were four complete recoveries in our series and twenty-one in the entire group. The material is presented under the following headings:

Spontaneous remission reported in the literature.

Recovery from the use of sulfonamide drugs.

Recovery from use of "combined methods," i. e. the combination of sulfonamide therapy and other measures (i. e. heparin; physical hyperthermia; intravenous typhoid-paratyphoid; radiotherapy).

*Spontaneous Remissions.* — Spontaneous recoveries from subacute bacterial endocarditis due to Streptococcus viridans or nonhaemolyticus are reported by Horder,[8] Murray,[9] Capps,[10] Libman,[11] Bögendoerfer,[12]

6. Ratish, H. D.; Davidson, A., and Bullowa, J. G. M.: The Absorption and Excretion of Sulfapyridine and of Sodium Sulfapyridine in Man, J. Pharmacol. & Exper. Therap. **69**: 364, 1940.

From the Medical Division, Service of Dr. George Baehr and the Department of Physical Therapy, the Mount Sinai Hospital. Material presented at the Scientific Exhibit of the Graduate Fortnight of the New York Academy of Medicine on "Infections," October 1940.

1. Krusen, F. H.: Present Status of Fever Therapy Produced by Physical Means, J. A. M. A. **107**: 1215 (Oct. 10) 1936.

2. Dry, T. J., and Willius, F. A.: Fever Therapy for Subacute Bacterial Endocarditis, Proc. Staff Meet., Mayo Clin. **12**: 321 (May 26) 1937.

3. Bierman, William, and Baehr, George: The Use of Physically Induced Pyrexia and Chemotherapy in the Treatment of Subacute Bacterial Endocarditis, this issue, p. 292.

4. Krusen, F. H., and Bennett, R. L.: Unsuccessful Treatment of Subacute Bacterial Endocarditis with Combined Fever and Sulfanilamide Therapy, Proc. Staff Meet., Mayo Clin. **15**: 328 (May 22) 1940.

5. White, H. J.: The Relationship Between Temperature and the Streptococcidal Activity of Sulfanilamide and Sulfapyridine in Vitro, J. Bact. **38**: 549 (Nov.) 1939.

6. Solomon, H. A.: Subacute Bacterial Endocarditis: Treatment with Sulfapyridine and Intravenous Injections of Typhoparatyphoid Vaccine, New York State M. J. **41**: 45 (Jan.) 1941; personal communication to the authors.

7. A single case of Bacillus influenzae (Haemophilus influenzae) endocarditis was included.

8. Horder, T.: Infective Endocarditis, Quart. J. Med. **2**: 289, 1908-1909.

9. Murray, L. M.: Subacute Bacterial Endocarditis, Ann. Clin. Med. **1**: 18, 1922.

10. Capps, J. A.: The Arsenical Treatment of Chronic Infectious Endocarditis, Am. J. M. Sc. **165**: 40 (Jan.) 1923.

11. Libman, Emanuel: A Consideration of the Prognosis in Subacute Bacterial Endocarditis, Am. Heart J. **1**: 25 (Oct.) 1925.

12. Bögendoerfer, L.: Zur Prognose der Endocarditis lenta, Deutsches Arch. f. klin. Med. **154**: 60, 1927.

Schottmueller,[13] Libman,[14] Kissling,[15] Middleton and Burke.[16] There are series of cases, however, in which no spontaneous recoveries have been noted (Warren and Herrick,[17] Thayer,[18] Capps,[19] Major [20]).

The most favorable outlook for spontaneous recovery from subacute bacterial endocarditis may be found in Libman's [11] study of his first 150 cases of the disease (of the "usual type of severity"). In this group of cases carefully studied and followed there were four complete recoveries, or 3 per cent. In a subsequent report Libman [14] enumerated twelve recoveries in patients "with the usual type" of the disease in a total of 1,000 cases. Three per cent probably represents the most favorable incidence of spontaneous recovery.

*Recovery from the Use of Sulfonamide Drugs.*—Isolated, successfully treated cases have been reported by McQuarrie,[21] Barton and Stinger,[22] Heyman [23] and Christie.[24] Recoveries occurring among groups of cases of subacute bacterial endocarditis treated with the sulfonamide drugs have also been reported by Major and Leger [25] and Major.[20] Long [26] to date has treated 117 patients with the sulfonamide drugs with seven recoveries. In our own series, 22 cases of subacute bacterial endocarditis were treated with one recovery. Isolated cases treated unsuccessfully (Barnett, Hartman, Perley and Ruhoff,[27] Sailer [28]) as well as groups of cases treated unsuccessfully have been reported (Klee and Römer,[29] Ellis,[30] Whitby,[31] Bliss, Long and Feinstone,[32] Kinell and Ernstene,[33] Kolmer,[34] Steele [35]).

The results of sulfonamide chemotherapy have been tabulated (table 2). In a total of 198 cases reported in the literature and those in our series recovery occurred in 12, or 6 per cent. Four additional isolated cases of recovery have been reported, totaling 16. The percentage of recovery including the latter 4 cases cannot be stated, however, as the total number of cases treated is not known.

*Recovery from Treatment with Combined Methods, i. e. the Combination of Sulfonamide Therapy and Other Measures.*—Under this heading are included cases that have been adequately treated by chemotherapy and some additional form of therapy.

TABLE 1.—*Spontaneous Recoveries in Subacute Bacterial Endocarditis*

| | Number of Cases | Number of Recoveries | Percentage of Recoveries |
|---|---|---|---|
| 1. Libman [11] | 150 | 4 | 3% |
| 2. Horder [8] | 150 | 1 | ... |
| 3. Thayer [18] | 206 | 0 | ... |
| 4. Warren and Herrick [17] | 25 | 0 | ... |
| 5. Major [20] | 15 | 0 | ... |
| 6. Middleton and Burke [16] | 88 | 1 | ... |
| Total | 634 | 6 | 1% |

A. Chemotherapy Combined with Heparin: There are 43 cases in this group. Kelson and White [36] treated 26 patients with combined sulfonamide and heparin, and 4 patients recovered. This series includes the 6 cases originally reported by these authors. Deitrick [37] treated 4 patients at the New York Hospital with no recoveries. Thirteen of the patients in our series were treated in this fashion with one recovery.[38] Of the total of 43 patients treated, 5, or 11.5 per cent, recovered (table 3). Only those patients who received physiologically active heparin adequate in dosage to produce prolongation of the blood coagulation time to over an hour were selected for this study. Kelson and White [39] have emphasized that heparin therapy should be instituted after chemotherapy has sterilized the blood stream.

B. Chemotherapy Combined with Hyperthermia: A total of 25 patients have been treated in this manner. Four of the entire series, 16 per cent, recovered (table 3). Six of the cases were treated unsuccessfully by Krusen and Bennett.[4] Ferderber [40] treated 3 cases with two successful results. Bierman and Baehr have observed two recoveries in a group of 16 cases treated at the Mount Sinai Hospital. One of the patients in this series who recovered had previously received six radium exposures over the precordium without clinical effect.[3]

Bierman stresses the necessity of "adequate" treatment. This can be defined empirically as at least eight sessions of hyperthermia in view of the fact that the 2 patients who recovered following this form of treatment received eight or more treatments. It should be noted that 1 patient who recovered suffered from Bacillus influenzae (Haemophilus influenzae) endocarditis. The hyperthermia should be induced on alter-

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14. Libman, Emanuel: A Further Report on Recovery and Recurrence in Subacute Bacterial Endocarditis, Tr. A. Am. Physicians **48:** 44, 1933.

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16. Middleton, W. S., and Burke, M.: Streptococcus Viridans Endocarditis Lenta: A Clinicopathologic Analysis of the Experience in the Wisconsin General Hospital, Am. J. M. Sc. **198:** 301 (Sept.) 1939.

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18. Thayer, W. S., in Symposium on Endocarditis, J. A. M. A. **82:** 1721 (May 24) 1924.

19. Capps, J. A.: Subacute Bacterial Endocarditis Due to Streptococcus Viridans with Special Reference to Prognosis, Ann. Int. Med. **13:** 280 (Aug.) 1939; cited by Kelson and White.[39]

20. Major, R. H.: The Effect of Sulfanilamide Compounds on Endocarditis, Am. J. M. Sc. **199:** 759 (June) 1940.

21. McQuarrie, I.: Report of Cases Treated with Sulfanilamide (Prontosil and Prontylin): Department of Pediatrics, University of Minnesota, J. Pediat. **11:** 188 (Aug.) 1937.

22. Barton, R. L., and Stinger, D.: Subacute Bacterial Endocarditis Treated with Sulfanilamide, J. Iowa State M. Soc. **29:** 402 (Aug.) 1939.

23. Heyman, Jacob: Subacute Bacterial Endocarditis Successfully Treated with Sulfanilamide: Report of Well Established Case Eighteen Months After Recovery, J. A. M. A. **114:** 2373 (June 15) 1940.

24. Christie, Amos: Subacute Bacterial Endocarditis Apparently Cured with Sulfanilamide, J. A. M. A. **115:** 1357 (Oct. 19) 1940.

25. Major, R. H., and Leger, L. H.: Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, J. A. M. A. **111:** 1919 (Nov. 19) 1938; Recovery from Subacute Infectious Endocarditis, J. Kansas M. Soc. **40:** 324 (Aug.) 1939.

26. Long, P. H.: Personal communication to the authors, 1940.

27. Barnett, H. L.; Hartman, A. F.; Perley, A. M., and Ruhoff, M. B.: Treatment of Pneumococcic Infections in Infants and Children with Sulfanilamide, J. A. M. A. **112:** 518 (Feb. 11) 1939.

28. Sailer, S.: Subacute Bacterial Endocarditis Treated with Sulfanilamide Resulting in Granulocytopenia and Death, Am. J. Clin. Path. **9:** 269 (May) 1939.

29. Klee, P., and Römer, H.: Prontosil bei Streptokokkenerkrankungen, Deutsche med. Wchnschr. **61:** 253 (Feb. 11) 1935.

30. Ellis, G. R.: Treatment of Subacute Bacterial Endocarditis with M. & B. 693, Lancet **2:** 1521 (Dec. 31) 1938.

31. Whitby, L.: Chemotherapy of Bacterial Infections, Lancet **2:** 1095 (Nov. 10) 1938.

32. Bliss, Eleanor A.; Long, P. H., and Feinstone, W. H.: The Differentiation of Streptococci and Its Relation to Sulfanilamide Therapy, South. M. J. **31:** 303 (March) 1938.

33. Kinell, J., and Ernstene, A. C.: Subacute Bacterial Endocarditis Treated Unsuccessfully with Sulfapyridine, Cleveland Clin. Quart. **7:** 83 (April) 1940.

34. Kolmer, J. A.: Progress in Chemotherapy of Bacterial and Other Diseases, with Special Reference to the Prontosils, Sulfanilamide and Sulfapyridine, Arch. Int. Med. **65:** 671 (April) 1940.

35. Steele, H. H.: Effect of Sulfanilamide on Length of Life of Patients with Subacute Bacterial Endocarditis, New England J. Med. **222:** 1067 (June 27) 1940.

36. Kelson, S. R., in discussion, Conference of the Medical Services on "Results in the Treatment of Subacute Bacterial Endocarditis by Recent New Methods," Mount Sinai Hospital, New York, May 15, 1940; personal communication to the authors. Kelson and White.[39]

37. Deitrick, John: Personal communication to the authors, 1940.

38. Kelson supervised the treatment of this patient at the Mount Sinai Hospital. It is included in this series with the permission of Dr. Elmer Gais.

39. Kelson, S. R., and White, P. D.: A New Method of Treatment of Subacute Bacterial Endocarditis, Using Sulfapyridine and Heparin in Combination: Preliminary Report, J. A. M. A. **113:** 1700 (Nov. 4) 1939.

40. Ferderber, M. B.: Personal communication to Dr. Bierman, 1940.

nate days, temperatures as high as 104 and 106 F. being maintained for periods of five hours and longer. The reaction of the patient may make it necessary to modify these factors.

C. Chemotherapy Combined with Intravenous Typhoid-Paratyphoid Vaccine: Solomon [6] has employed chemotherapy and hyperpyrexia induced by the intravenous use of typhoid-paratyphoid vaccine in 17 cases with five recoveries. His technic was used in the treatment of 4 patients in our series with unsuccessful results. Of the combined total of 21 cases treated in this manner 5, or 25 per cent, recovered (table 3).

TABLE 2.—*Results of Sulfonamide Chemotherapy in Subacute Bacterial Endocarditis*

| | Number of Cases | Number of Recoveries |
|---|---|---|
| 1. Major [20] | 7 | 3 |
| 2. Kinell and Ernstene [33] | 5 | 0 |
| 3. Spink and Crago: Arch. Int. Med. 64: 228 (Aug.) 1939 | 11 | 1 |
| 4. Klee and Römer [29] | 4 | 0 |
| 5. Ellis [30] | 2 | 0 |
| 6. Whitby [31] | 3 | 0 |
| 7. Bliss, Long and Feinstone [32] | 3 | 0 |
| 8. Kolmer [34] | 10 | 0 |
| 9. Steele [35] | 14 | 0 |
| 10. Long [26] | 117 | 7 |
| 11. Mount Sinai | 22 | 1 |
| Total | 198 | 12 |
| Per cent recovery | 6.0 | |

The use of intravenous typhoid-paratyphoid vaccine to increase the fever level was used by Solomon in preference to artificial hyperpyrexia because he believes that "by combining foreign protein shock therapy with the sulfonamides the effectiveness of the drug is enhanced not only by the hyperpyrexia produced which in itself renders the drug bactericidal instead of bacteriostatic but also by the addition of many factors in the immunity, some not clearly understood, which are activated at the same time." He states that adequate treatment by this method consists of at least six sessions of hyperpyrexia induced by graduated doses of the vaccine. These injections should be given over a period of seven to ten days. Leukopenia and latent jaundice may follow the use of intravenous injections of typhoid bacilli combined with the use of sulfonamide drugs. It is important to differentiate the leukopenia caused by the intravenous typhoid vaccine from that produced by the toxic action of the sulfonamide drugs. In the 4 cases treated in this manner in our series, chemotherapy was continued despite the neutropenia but the intravenous injections were temporarily discontinued until the leukocyte picture returned to normal.

TABLE 3.—*Results with Combined Methods of Treatment of Subacute Bacterial Endocarditis*

| | Number of Cases | Number of Recoveries | Percentage of Recoveries |
|---|---|---|---|
| Chemotherapy, heparin | | | |
| 1. Kelson and White * | 26 | 4 | |
| 2. New York Hospital [37] | 4 | 0 | |
| 3. Mount Sinai | 13 | 1 † | |
| | 43 | 5 | 11.5 |
| Chemotherapy, hyperthermia | | | |
| 1. Krusen and Bennet | 6 | 0 | |
| 2. Ferderber [40] | 3 | 2 | |
| 3. Mount Sinai | 16 | 2 ‡ | |
| | 25 | 4 | 16.0 |
| Chemotherapy, intravenous typhoid | | | |
| 1. Solomon, H. A., to be published | 17 | 5 | |
| 2. Mount Sinai | 4 | 0 | |
| | 21 | 5 | 25 |
| Chemotherapy, radiotherapy | | | |
| Mount Sinai # | 6 | 1 § | 16.5 |
| Total | | | |
| Literature | 56 | 11 | 20.0 |
| Mount Sinai | 33 | 3 | 9.5 |
| | 89 | 14 | Av. 16.0 |

* Includes six cases in original report.
† Case of recovery also referred to in Kelson and White series.
‡ An additional patient is now bacteria free and afebrile for a period of four months.
# All patients in this group also treated by other measures.
§ Also treated with hyperthermia; included in two recoveries noted above under this heading.

D. Chemotherapy Combined with Radiotherapy: Six patients received radiotherapy over the precordium in addition to chemotherapy. The only patient in this group who recovered also received nine treatments with artificial hyperpyrexia. The blood cultures remained positive despite the radiotherapy. The blood cultures became negative following the hyperthermia treatments.

TABLE 4.—*Summary of Results of Treatment of Subacute Bacterial Endocarditis* *

| Method of Treatment | Number Treated | Number Recovered | Percentage Recovered |
|---|---|---|---|
| Chemotherapy † alone | | | |
| Mount Sinai | 22 | 1 | 4.5 |
| Literature | 176 | 11 | 6.0 |
| | 6§ | 4§ | |
| Total | 198 | 12 | 6.0 |
| | 6§ | 4 | |
| Combined therapy ‡ | | | |
| Mount Sinai | 32 | 3 | 9.5 |
| Literature | 56 | 11 | 20.0 |
| Total | 88 | 14 | 16.0 |
| Total cases | | | |
| Mount Sinai | 54 | 4 | 7.5 |
| Literature | 232 | 22 | 9.5 |
| | 6 | 4 | |
| Total | 286 | 26 | 9.0 |
| | 6§ | 4§ | |

* Viridans and nonhemolytic streptococcus cases (one case due to Bacillus [Haemophilus] influenzae with recovery included). Maximum incidence of spontaneous recovery 3 per cent (Libman).
† Sulfonamide compounds (sulfanilamide, sulfapyridine, sulfathiazole).
§ Individual case reports (four recoveries, 2 deaths).
‡ Chemotherapy combined with (1) heparin, (2) radiotherapy, (3) hyperthermia, (4) intravenous typhoid-paratyphoid (Solomon).

It is improbable that the radiotherapy contributed to the recovery. Two patients who had chemotherapy and radiotherapy and no other procedure failed to recover. Three others treated in this manner with additional artificial hyperthermia also failed to recover.

## COMMENT

Reports of isolated examples of recovery from subacute bacterial endocarditis after one form of therapy or another do not permit a comparison of the effectiveness of the various therapeutic procedures or an evaluation of the role played by spontaneous recovery. For this reason we are including only the results observed in reported series.

The best prospect for spontaneous recovery has been 3 per cent (Libman). The incidence of recovery from subacute bacterial endocarditis due to Streptococcus viridans and nonhaemolyticus approximates 6 per cent following treatment with the sulfonamide drugs. Chemotherapy combined with additional forms of treatment such as heparin, artificial hyperthermia and intravenous injection of typhoid-paratyphoid vaccine yields an incidence of recovery over twice as large as that obtained with the sulfonamide drugs alone (table 4). The series of cases reported is still too small to

arrive at any final conclusion as to the value of these methods of treatment of the disease. It is apparent however that in the treatment of the active phase of the disease the newer forms of treatment promise a better chance for recovery than do the methods employed heretofore.

Clinical observations support the in vitro observations of White [5] that the addition of some form of hyperthermia to chemotherapy promotes the efficacy of the latter.

The present study warrants no definite statement as to choice of sulfonamide drug in the treatment of subacute bacterial endocarditis. Greater experience has been had to date with the use of sulfanilamide and sulfapyridine than with sulfathiazole. Favorable results have definitely been obtained with the first two of these drugs in Streptococcus viridans endocarditis. The former drug is better tolerated. The preference at this time appears to be for sulfapyridine. If the patient develops so-called sulfapyridine fastness, intolerance or toxicity and sulfonamide medication is to be continued, it is advisable to change to sulfanilamide. Sulfathiazole is best employed from the outset in cases of endocarditis due to unusual organisms, e. g. B. hoffmanii.

Optimal results may be expected from adequate treatment given at the optimum time. Early diagnosis and early intensive treatment favor recovery. Leukopenia and normal temperature are factors which decrease the bacteriostatic and bactericidal effects of the drugs. Kelson and White have recommended that heparin should first be administered after chemotherapy has rendered the blood sterile. Results from the methods producing hyperthermia may be improved by their early administration within twenty-four to forty-eight hours after chemotherapy is begun. It is advisable to maintain the hyperpyrexia for at least five hours and to repeat the treatments on alternate days if tolerated. The prospect of recovery with the combined methods of treatment may be further increased if more attention is paid in the future to the factors which enhance the effects of chemotherapy.

SUMMARY

Among 200 cases of subacute bacterial endocarditis due to Streptococcus viridans and nonhaemolyticus collected from the literature and the records of the Mount Sinai Hospital, in which the sulfonamide drugs were administered, recovery occurred in 12, an incidence of 6.0 per cent recovery.

Among 43 patients treated with combined chemotherapy and heparin 5 recovered, an incidence of 11.5 per cent recovery.

Among 24 patients treated by chemotherapy and physically induced hyperthermia 4 recovered, an incidence of 16.0 per cent recovery. Of 21 patients treated by chemotherapy and hyperthermia induced by intravenous typhoid-paratyphoid vaccine 5 recovered, an increase of 25 per cent recovery.

The number of cases in the three series treated by combined methods is still too small to yield an accurate statistical estimate of the incidence of recovery in each group. This preliminary review of the results obtained thus far is encouraging. The combined methods of therapy seem to promise a greater incidence of recovery than may be anticipated in the natural course of the disease or after treatment with the sulfonamide drugs alone.

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# LEPTOSPIROSIS: A PUBLIC HEALTH HAZARD

## REPORT OF A SMALL OUTBREAK OF WEIL'S DISEASE IN BATHERS

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About fifty years ago Weil [1] discovered an acute infectious disease with jaundice and fever to which his name was later applied. In 1914 Inada and Ido [2] proved the etiologic agent to be a spiral shaped micro-organism which Noguchi [3] shortly thereafter described in detail, naming it Leptospira icterohaemorrhagiae.

Since the identification of this micro-organism there has gradually accumulated knowledge of other morphologically similar but serologically and immunologically different members of the same group of leptospiras.[4] They are distributed worldwide and are usually associted with rats and dogs. Many of them classed as Leptospira biflexa [5] are not pathogenic for man. In Europe at least three distinct pathogenic varieties are recognized: (1) Leptospira icterohaemorrhagiae of Weil's disease, (2) Leptospira canicola [6] of an infection in dogs transmissible to man and (3) Leptospira grippo-typhosa [7] of a syndrome known in different places as "summer influenza," "harvest fever," "mud fever," "water fever" or "swamp fever." Another variant, Leptospira hebdomadis, discovered by Ido and Ito,[8] is the cause of the "seven day fever" of Japan. Although infections caused by Leptospira grippo-typhosa and Leptospira hebdomadis have not been reported in the United States, it is probable that they occur here, since Leptospira icterohaemorrhagiae, Leptospira canicola [9] and Leptospira biflexa are present. The best discussion of the subject has been published by Walch-Sorgdrager.[10]

Outbreaks of disease due to pathogenic leptospiras constantly occur throughout the world. In 1938, for example, an epidemic of Weil's disease broke out among rice field workers in Italy,[11] and hundreds of cases of "field fever" were said to have occurred among har-

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10. Walch-Sorgdrager, B.: Leptospiroses, Bull. Health Organ., League of Nations **8:** 143-386, 1939.

11. Mino, Prospero: Ueber Leptospirosen bei den Arbeitern der Reisfelder Oberitaliens, Ztschr. f. Immunitätsforsch. u. exper. Therap. **96:** 466-520 (Oct. 2) 1939.

vesters in Bavaria.[12] In one group[12a] the leptospiras were identical with L. bataviae from Java, where the disease, as in Italy, occurs in rice harvesters. It is probable that these outbreaks resulted from contact of large numbers of field workers in late summer with water contaminated with rat urine.

Except for severity, the various leptospiroses are usually clinically indistinguishable. The form called Weil's disease caused by Leptospira icterohaemorrhagiae is regarded as the most severe, since about 50 per cent of cases are said to present jaundice. In contrast, jaundice was present in only 2 per cent of Rimpau's[13] cases of "field fever" caused by Leptospira grippo-typhosa.

Although the first proved cases of Weil's disease in Great Britain[14] and in the United States[15] were reported in the same year, 1922, subsequent reports give the impression that the disease is much more common in Great Britain than it is here, which there is reason to doubt. For example, between 1922 and 1939, 248[16] proved cases have been recorded by British observers but only about twenty-three in this country. The large number of cases recognized abroad may be partly attributed to a greater interest in the disease

Leptospira icterohaemorrhagiae in liver of a guinea pig inoculated with patient's blood. Levaditi's stain, × 1,000.

there and to the recognition of the milder, nonicteric forms of the disease. The latter point is of especial importance, and because of it it is necessary to revise our criteria of the "classic" case of Weil's disease. It is most likely that the striking, easily recognized forms with jaundice, hemorrhage and fever are only the severest forms of an infectious disease which is usually mild and therefore unrecognized. It is probable that, as in other infectious diseases, the mild forms far outnumber the severe ones. This being true, Weil's disease may be arbitrarily graded into (*a*) subclinical or mild ambulatory forms, (*b*) moderately severe icteric or nonicteric forms and (*c*) severe, often fatal, forms with jaundice and bleeding. It is evident that without the use of serologic, cultural or other tests the mild forms may be mistaken for other diseases, especially influenza, since an acute onset with a chill, fever, pain in the limbs, headache and conjunctival injection are usually present.

We believe that the leptospiroses are much more common in the United States than is generally believed. Cases have been reported from many isolated parts of the country, most recently from New Jersey and Pennsylvania[17] and from California,[9] where Leptospira canicola has been found in dogs. No doubt in many cases the diagnosis is missed, especially if visible jaundice is absent, and even when the diagnosis is made the disease, not being a "reportable" one, is usually not listed in vital statistics. We know of a number of unreported cases in Philadelphia.

Weil's disease affects chiefly workers in certain occupations. For example, in Great Britain[18] the disease occurs most often among fish handlers, coal miners and sewer workers, each of whom work in environments often infested with rats, the natural source of the disease. Bathing in water presumably polluted with rat excreta is the fourth most common mode of infection in Great Britain,[19] and, according to Walch-Sorgdrager,[10] 78 per cent of patients in Holland were infected in this manner. Schüffner[20] stresses the role of struggling and inhalation of water incident to submersion or of using the "crawl" stroke in swimming as factors favoring infection. Infection may also be acquired by drinking contaminated water, as illustrated by the outbreak of Weil's disease in Lisbon in 1931.[21]

To emphasize the danger of bathing in possibly contaminated water, a small outbreak which occurred in July 1939 is described. Seven young men swam in a public bathing pool formed by a dam in a creek near Philadelphia. The pool was adjacent to cattle barns and refuse pits which were infested with rats. From four to twelve days after swimming, each of these men became sick in varying degrees of severity.

### REPORT OF CASES

Of the seven patients, two were sick enough to require hospital care and one of these died. Of the five patients with mild attacks, two were obliged to spend several days in bed but the other three were ambulatory.

CASE 1.—J. C. had chills followed by fever and intense frontal headache six days after swimming. Malaise, weakness and pains in the legs were severe enough to require a week's rest in bed. There was anorexia but no jaundice or vomiting. Convalescence was rapid.

CASE 2.—V. P. was taken with malaise, general weakness, aching and anorexia one week after swimming. There was no jaundice. Recovery was rapid after two days spent in bed.

CASES 3, 4 and 5.—The symptoms were those of chilliness, headache, weakness, anorexia and pains in the legs for from several days to a week. The symptoms are indeed not specific but are the same as those of the cases of mild involvement studied in Europe. The patients were ambulatory. The same symptoms were also present in the two cases of severe involvement but were much more pronounced and accompanied with jaundice, bleeding and high fever.

CASE 6.—E. Z. aged 24 (record by courtesy of Dr. E. P. Reif) was admitted to the Methodist Episcopal Hospital July

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24, 1939. Four days before admission and four days after swimming he had a shaking chill followed by malaise, weakness and fever. He was somewhat better the following morning, although his temperature was 38.3 C. (101 F.) On admission on the fourth day of his illness he complained of severe pain in the left side of the face radiating to the forehead, malaise, weakness and a sense of oppression in the chest.

The patient was well developed and well nourished and was acutely ill. His face was flushed and his throat was injected. Breath sounds were suppressed, resonance was impaired and rales were present in the lower portion of the right lung. On the left side a few crackling rales were heard at the base of the lung. The heart rate was rapid and regular. The abdomen was distended but the liver and spleen were not felt. Reflexes were physiologic. The hemoglobin content measured 76 per cent and the erythrocytes numbered 3,800,000 and the leukocytes 18,600. There were albuminuria, hematuria and bile in increased amounts in the urine. The direct van den Bergh test gave a positive reaction and the icterus index was 102. The blood urea nitrogen was 120 mg. and the Wassermann reaction was negative. A roentgenogram of the chest revealed patches of increased density over both lung fields, interpreted as pneumonia.

During the ensuing eight days the patient became worse. The jaundice, hematuria and nitrogen retention increased. Slight nuchal rigidity appeared and he vomited bloody material on several occasions. There was tenderness over the liver, which became palpable from one to two fingerbreaths below the costal border. During this time the temperature declined by lysis to normal, remaining so for four days, and then rose again to 40.5 C. (105 F.), with daily fluctuations for the next three weeks, during which the patient gradually improved with the jaundice and hematuria diminishing. He left the hospital well except for slight jaundice five weeks after admission.

CASE 7.—*History.*—A. N., aged 26, went to bed feeling chilly and weak six days after he had been swimming. The next day he felt better and got up but soon returned to bed. There were anorexia, constipation and fever. He was admitted to the hospital on the fourth day of his illness complaining of severe headache, pains throughout the body, weakness and cough.

The patient was well developed and well nourished; he was dyspneic, cyanotic and intensely jaundiced. The temperature was 38.9 C. (102 F.), pulse rate 122, respiratory rate 36, blood pressure 122 systolic and 78 diastolic. The conjunctivas were injected, the nose was bleeding and there were excoriations along the nasal septum. Over the right lower and middle lobes of the lung the breath sounds and resonance were impaired. Tactile fremitus and vocal resonance were increased. There were medium and fine rales extending to the infraclavicular region and to the scapula posteriorly. The heart was slightly enlarged with a systolic murmur at the apex. There was areflexia in the lower extremities and distal hyperalgesia. The hemoglobin measured 50 per cent, the erythrocytes numbered 2,600,000 and the leukocytes 28,000. There were heavy albuminuria and hematuria, and urobilinogen was positive in a dilution of 1:400. The serum bilirubin was 18.2 mg. with a positive direct van den Bergh reaction, with 70 per cent bromsulphalein dye retention. The Wassermann reaction was negative. A roentgenogram of the chest revealed increased density over the right middle and lower lobes of the lungs, interpreted as pneumonia.

The patient rapidly became worse; jaundice and hematuria increased. Evidence of consolidation spread to the left lung. Subconjunctival hemorrhages appeared, the temperature decreased and the patient died on the seventh day of illness.

The chief abnormalities noted by Dr. M. M. Lieber post mortem were generalized icterus, a peculiar irregular type of consolidation due to extensive hemorrhage in both lower lobes of the lungs, splenomegaly, acute hepatitis and acute ulcerative gastroduodenitis. Histologically there was leptospirosis of the liver and kidneys.

*Biologic Study.*—On the sixth day of illness the patient's blood and urine were examined by the dark field method for the presence of leptospiras but none were found. At the same time 5 cc. of citrated blood of the patient was injected intraperitoneally into each of four guinea pigs. Two animals died soon after but the other two developed a temperature of 40.5 C. (105 F.) six days later, became jaundiced on the seventh day and died on the ninth. Leptospira icterohaemorrhagiae was found in sections of the liver and kidneys when stained by Levaditi's method, as shown in the accompanying illustration. Blood taken from these animals during their illness caused similar disease when injected into fresh guinea pigs. Leptospiras were cultivated from the blood when incubated in Manteufel's medium.

Attempts were later made to prove the diagnosis of Weil's disease in the six other members of the party who had been sick at the same time. Blood was taken from each about fifty days after his attack and sent to Dr. Packchanian of the National Institute of Health, who tested the serum for the presence of agglutinins for Leptospira icterohaemorrhagiae. Specific agglutinins were present in a titer of 1:10,000 in case 6 but were absent in serum from the patients who had had mild attacks.

## COMMENT

Although proof of Weil's disease was not established in the mild cases of the outbreak, it is highly probable that all the men suffered from the same disease. They swam together in a pool likely to have been polluted with rat excrement, they became sick at about the same time afterward and most of their symptoms were similar except in the degree of severity. The fact that no agglutinins were demonstrable in the blood of the mildly sick patients, fifty days later, although failing to prove the diagnosis, does not detract from it. Rimpau has shown that, as in other infections, specific agglutinins may never develop or they may disappear within a few weeks, particularly in mild cases of field fever. We requested permission to catch some of the rats in the vicinity of the pool, but the owner of the premises was loath to give it, so that studies could not be made.

## SUMMARY

In July 1939 seven young men bathing in a stream probably polluted by infected rats contracted an acute infectious disease in varying grades of severity. Five were affected mildly and two were severely sick, one of whom died. Cultural studies in the fatal case and serologic evidence in the other severe case proved a diagnosis of leptospirosis icterohaemorrhagica. Clinical and epidemiologic evidence favored a similar diagnosis in the mild cases, although serologic confirmation was not obtained.

The possible danger of contracting leptospirosis by bathing in ponds likely to be polluted by rats and of drinking polluted water should be kept in mind.

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**Development of Cold Storage.**—A schoolteacher, Benjamin Nyce, is to be credited with the invention of a satisfactory system of cold storage. In 1857 he erected near his home a small insulated building divided into two compartments by a horizontal sheet of iron. The upper compartment was filled with ice, the lower used for the storage of provisions, and all important facilities for adequate ventilation and the absorption of excess moisture were provided. This device—in essence a gigantic icebox—was patented by Nyce in 1858. So successful was his plan and so large were the profits in the handling of out of season fruits that use of the method spread widely. Substitution of mechanical refrigeration for natural ice in the 1870's made storage on a large scale possible, and by the close of the century the number of storage houses for fruit and vegetables located in the smaller cities and towns was increasing rapidly.—Cummings, Richard Osborn: The American and His Food, Chicago, University of Chicago Press, 1940.

# THE USE OF PHYSICALLY INDUCED PYREXIA AND CHEMOTHERAPY

## IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

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An elevation of temperature increases the intensity of chemical reactions. This has been demonstrated in vivo by the improved therapeutic results following the use of elevation of body temperature when sulfanilamide is employed to kill that relatively fragile bacterium the gonococcus.[1] It has been demonstrated in vitro for the hemolytic streptococcus by White,[2] who showed that the bacteriostatic power of sulfanilamide is about one hundred times greater at 39 C. than at 37.2 C.

We have had the opportunity of applying a combination of chemotherapy (sulfanilamide or sulfapyridine) and physically induced elevation of body temperature to cases of subacute bacterial endocarditis. Out of 16 patients each of whom received six or more bouts of temperature elevation in conjunction with medication, but 2 have made recoveries. In still another typical case the blood cultures which were consistently positive for Streptococcus viridans have been negative for the past four months. This patient seems also to have recovered. However, this period of follow-up is too short to permit us to include him in our present series.

This record is certainly not a brilliant one. However, in a disease which is usually fatal, the fact that two recoveries did occur challenges attention. Libman [3] states that spontaneous recovery occurs in 3 per cent of cases. In contrast, the results in our series are statistically better than this, but the number of our patients is too small to be challenging. Long and Bliss [4] have reported five apparent cures in 60 cases following the use of sulfonamide therapy alone. In 22 of our own cases there has been one recovery following the use of chemotherapy without pyrexia.

Because of their unusual therapeutic sequelae, a description of our 2 cases in which recovery occurred may be of interest:

CASE 1.—A man aged 32 suffered from subacute bacterial endocarditis due to Streptococcus viridans. Five weeks before admission to the hospital, he noted the development of sore throat and severe right frontal headache. The headache and sore throat abated after a few days, but the fever continued. The temperature was noted to be at about 100 F. in the morning, reaching 101-102.5 F. during the evening.

The patient was well developed and well nourished. He did not appear very ill. Examination of the heart revealed no enlargement. The sounds were of good quality; there was a blowing systolic murmur to the left of the sternum over the mitral area which was not well transmitted to the axilla. The blood pressure was 124 systolic and 70 diastolic. Abdominal examination was entirely negative. The liver and spleen were not felt. A moderate degree of clubbing of the fingers was noted. There were no petechiae, and examination of the fundi revealed no hemorrhages. On admission, hemoglobin was 85 per cent, white blood cells 13,500, polymorphocytes 79 per cent, of which 14 per cent were nonsegmented forms, lymphocytes 14 per cent, monocytes 7 per cent. No macrophages were seen in a smear of blood from the ear lobe. Sedimentation time was 55 minutes. Admission urine showed only a faint trace of albumin and an occasional white blood corpuscle. However, microscopic examination of the sediment of later urine showed occasional red blood cells and at times a few granular and cellular casts. An electrocardiogram showed a left ventricular preponderance with no abnormality of the ventricular waves to suggest myocardial damage. During the first week in the hospital the patient's temperature ranged between 99 and 101.8 F. Because of the presence of clubbing of the fingers and a systolic murmur at the apex, the diagnosis of subacute bacterial endocarditis was considered and blood cultures were taken. This impression was confirmed by the finding of Streptococcus viridans, two colonies per cubic centimeter, on the initial blood culture taken on Sept. 18, 1938, with a second report of Streptococcus viridans fifteen colonies per cubic centimeter on September 21. Although previous therapeutic attempts in this disease had not met with any success, it was decided to treat the patient with radiotherapy and then with a combination of sulfanilamide and hyperpyrexia. Accordingly, on September 30 radiotherapy was instituted and during the ensuing eight days the patient received six exposures, totaling 2,400 roentgens directed over the precordium. No subjective or objective improvement could be discerned during or immediately after this course of treatment. The temperature continued to range between 100 and 102.6 F. The urine continued to show the presence of red blood cells.

After the initial radium treatment the patient complained of a sudden onset of pain in the left temporal region. Over an anterior branch of the left temporal artery a tender, raised, slightly reddened area was noted. There was no distal discoloration, but no pulsation could be felt in the distal portion of the artery. It seemed most likely that this was either an embolization of a small arterial branch or a mycotic aneurysm. This lesion subsided with the application of wet dressings over the involved area. On October 7, after the last radium treatment, the patient complained of a sudden marked pain in the left side of his abdomen associated with nausea. The abdomen was soft throughout but there was tenderness on deep pressure, which was most marked at the left costovertebral angle. Although urinalysis following this episode showed only two to four red blood cells per high power field, a renal infarction was considered the etiologic factor for this pain. Again on October 11 the patient complained of generalized abdominal pain associated with nausea, and following this he vomited some undigested food. Simultaneously the temperature rose to 104.4 F. Examination revealed only moderate distention with deep diffuse tenderness. An embolic phenomenon was considered this time, perhaps to a small division of a mesenteric artery. On October 12, treatment with sulfanilamide was instituted and a total of 66 Gm. was given over a period of eleven days, a blood concentration of 9 mg. per hundred cubic centimeters of sulfanilamide being attained. During this period the patient appeared much more ill and his temperature ranged to higher levels, frequently reaching 104 F. Because of what appeared to be a toxic effect of sulfanilamide, and because of a drop of hemoglobin from 80 per cent to 65 per cent, the latter treatment was discontinued on October 22. On October 14, hyperpyrexia was started, and the patient received nine such treatments. The temperature was raised from 104 to 105.6 F. and was maintained at that level for between three and six hours. After discontinuance of the sulfanilamide the temperature ranged to lower levels, usually varying between 99 and 101 F. On November 1 a blood culture showed the presence of Streptococcus viridans in two flasks, and three colonies

From the Departments of Physical Therapy and Medicine of the Mount Sinai Hospital.

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were seen on the blood plate. Hyperpyrexia was continued from October 14 to November 8, at which date the last treatment was given. On November 12 a blood culture showed no growth, and subsequent blood cultures taken on November 17 and 25 and again on December 2 were also sterile. Simultaneously there was a marked improvement in the general condition of the patient; his temperature returned to normal levels, the hemoglobin rose from 65 to 90 per cent, there were no further embolic phenomena, and red cells disappeared from the urine. The cardiac murmur remained unchanged. Clubbing of the fingers, which was previously noted, completely disappeared within three weeks after the blood became sterile and the temperature normal. The patient has now been well and at work for more than two years.

CASE 2.—A girl aged 19 years had subacute bacterial endocarditis due to the bacillus of influenza. About two and one-half weeks before her admission to the hospital she had a severe chill, which lasted for one half hour and was followed by a temperature elevation to 104 F. accompanied by malaise, anorexia and a dull backache. She was then well for several days until six days before admission, when she again had a shaking chill. Following this she had an irregular temperature between 101 and 103 F. without localizing symptoms.

The patient was asthenic, poorly developed and nourished, sallow but not acutely ill. There was no cardiac enlargement. There was a low pitched, short, systolic murmur, not transmitted. No thrills were present. The sounds were of good quality; the second pulmonic sound was louder than the second aortic. The blood pressure was 110 systolic and 70 diastolic. The abdomen was soft and scaphoid. Loops of the bowel were easily palpable. The spleen was moderately firm, nontender and palpable two fingerbreadths from the left costal margin on deep inspiration. The hands were moist. Slight pain was experienced on motion of the right wrist. Hemoglobin was 68 per cent; the leukocyte count was 12,200, with segmented cells 68 per cent, nonsegmented 6 per cent, lymphocytes 24 per cent, monocytes 2 per cent. The sedimentation time was forty minutes. An electrocardiogram showed no abnormality. The urine was normal. Blood agglutination for typhoid and paratyphoid and Brucella melitensis was likewise negative.

During the first two weeks of her stay in the hospital, the patient's temperature ranged irregularly between 100 and 104 F. The pulse was relatively slow, averaging 90. The respiratory rate was 22. The body weight was 97 pounds (44 Kg.). The first three blood cultures revealed no growth but the fourth, taken when the temperature was 104 F., was positive for the influenza organism after two days' incubation under either aerobic or anaerobic conditions or under carbon dioxide. This organism needed blood, as was shown by its failure to grow in

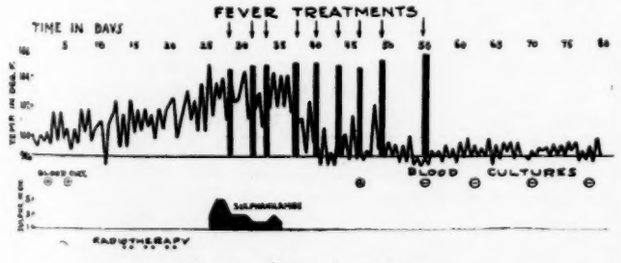


Fig. 1.—Course in case 1.

unenriched mediums. It reduced nitrate to nitrite and had the typical morphologic appearance of the influenza group. On primary culture it agglutinated in a dilution of 1:28 with stock anti-influenza serums, but after several transplants the agglutinability disappeared. The patient's serum and that of another patient with endocarditis due to a similar organism were extremely potent in agglutinating this organism. Titers higher than 1:1,000 were obtained.

The patient was started on sulfanilamide 6 to 8 Gm. daily for ten days. There was but little effect on the temperature curve. Blood cultures drawn when the blood sulfanilamide level was as high as 11 mg. per hundred cubic centimeters were recorded positive. The blood count at this time revealed the highest number of white blood cells recorded, 17,200, segmented polymorphocytes 61 per cent, nonsegmented 19 per cent, lymphocytes 15 per cent, monocytes 5 per cent. The patient was given numerous transfusions, despite which the hemoglobin did not rise above 80 per cent. During this period the systolic apical murmur became somewhat louder. A few hemorrhagic spots appeared on the fingers. These were interpreted as Janeway nodes. They were nontender and disappeared in a few days. The spleen became somewhat larger, and a few petechiae were noted in the buccal mucous membrane. At

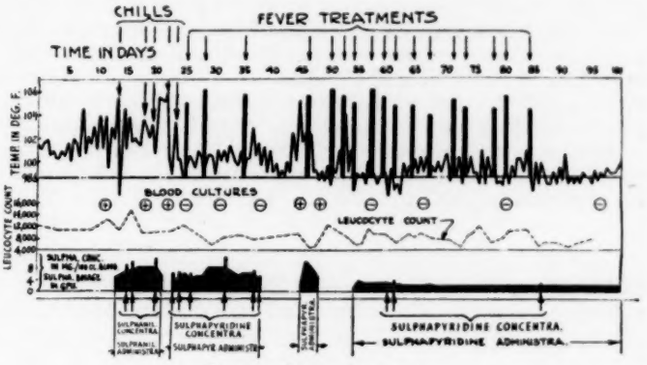


Fig. 2.—Course in case 2.

another period slight soreness of the throat was complained of, but there were no objective lesions. The only toxic manifestations to the administration of this drug were some nausea and occasional vomiting and marked cyanosis. Because of failure of sulfanilamide to affect the course, it was decided to switch to sulfapyridine 6 Gm. daily. This was later changed to 3 Gm. and a total of 99.5 Gm. was given in two and one-half weeks. During this time three physically induced fever treatments were administered. Two blood cultures drawn during this period were negative. The temperature ranged between 99 and 101 F. However, a week after the drug and the fever treatments were stopped, the culture again became positive and the temperature varied between 101 and 105 F.

In view of the fairly satisfactory response with the use of sulfapyridine and fever treatments previously, it was decided to start this regimen again. After several days, however, the white blood cell count dropped to 4,700, the temperature in the meantime falling to normal. The drug was discontinued for six days, but the fever applications were continued. The administration of sulfapyridine was started again, 2 Gm. daily, the blood count being followed carefully. The response to this regimen was excellent. The temperature fell to normal limits and varied between 101.5 and 98 F. for the next four weeks. In the last two weeks of her hospital stay, the highest temperature was 99.8 F. Two blood cultures during this period revealed no growth. The white blood cell count remained 8,000 with normal differential. The hemoglobin was kept to 75 per cent by occasional blood transfusions. A blood level of 3 mg. per hundred cubic centimeters of sulfapyridine could be maintained with this small dosage. In all, 99 Gm. of sulfapyridine was given during a six weeks period. Appetite was good and there was a gradual gain in weight. Embolic phenomena were no longer noticed. The spleen receded in size but was still palpable at the time of discharge. The systolic cardiac murmur almost entirely disappeared. The generalized lymphadenopathy was no longer present, and the urine showed no abnormalities.

Early in the course of sulfapyridine administration, when the temperature fell to within relatively normal limits, it was decided to institute hyperthermia to increase the bactericidal activity of the blood and tissue. Accordingly the patient was given a course of sixteen sessions during which the body temperature was raised to between 105 and 106 F. for five hours. She withstood this therapy well. It was felt that the hemopoietic stimulating effect of hyperthermia contributed to the maintenance of a relatively normal blood count. About two weeks before discharge, the patient developed a left lower lobe pulmonary infarct, and roentgen examination of the chest

shortly after this revealed some elevation of the left leaf of the diaphragm and the presence of a small amount of fluid. At no time did the electrocardiogram reveal any definite abnormality. Several urine cultures did not show significant organisms; however, on two occasions Bacillus influenzae was recovered from a throat culture. Neither one of these was taken during a course of sulfapyridine. Roentgen examination of the paranasal sinuses failed to reveal any abnormality.

After discharge from the hospital the patient continued to take maintenance doses of sulfapyridine, 0.5 Gm. every six hours. Blood counts were taken periodically. During the month following her discharge from the hospital she gained 14 pounds (6.4 Kg.). There were no symptoms of drug intolerance, infection or diminished cardiac reserve. Blood cultures were negative. The administration of the drug was discontinued on June 4, 1940. Blood cultures continued negative and have remained so. She has been well for ten months. There is only the faintest trace of a systolic murmur at the apex. The spleen is barely palpable. There are no embolic phenomena. She indulges in active physical exercise.

## TECHNIC

The administration of physically induced pyrexia to patients suffering from subacute bacterial endocarditis presents special difficulties, as their cardiovascular system may show evidence of considerable damage. They therefore require particularly close watching. As in many instances they come for treatment with an elevation of temperature (100 to 103 F.) it is unnecessary to use as much conversive and conductive heating as in the treatment of other conditions. Otherwise the systemic temperature will climb too rapidly and to too high a level. The use of large doses of sulfanilamide before and during the pyrexia treatments may cause the patient to become a bluish gray, thus making it difficult to recognize the onset of cyanosis. The pulse rate is usually rapid, varying from about 130 to 160 beats per minute. In spite of the administration of morphine sulfate, patients are frequently very restless. Nausea, circumoral pallor and very rapid respiration are symptoms which may develop even though the temperature elevation be at a comparatively low level. These symptoms may be due to the severe cardiac involvement. We have also observed the development of a rash during the treatment or on the day following. This rash covers the entire body or is localized to the chest, hands and arms. Although the treatments are uncomfortable and require the use of sedation, it was of interest to note that the 2 patients who survived were not disturbed by the treatments given initially. On the contrary, they asked that the pyrexia sessions be administered because they felt so much more comfortable during and after them. Subsequently in the course of these treatments they began to object to them as do other patients.

## COMMENT

The results achieved in these 2 cases indicate to us the need for the further study of this method of treatment for subacute bacterial endocarditis. The problems which should be solved include the determination of the height and duration of the optimum temperatures to be induced and the optimum concentration of the drug in the blood. It has been shown that great variations in blood concentration occur which bear no exact relationship to the dosage of the drug.[5] Also the concentration of the drug differs in different parts of the body, having been found to be highest in the lungs, skin and kidneys. The initial decrease in systemic temperature and the negative cultures following the positive ones in the second case would tend to show that a bacteriostatic influence had been exerted on the blood by the treatment. It is possible that the verrucous deposits on the heart valves continued to harbor the micro-organisms which were not killed and which subsequently caused the blood cultures to become positive. The relatively avascular status of the verrucous deposits makes it difficult to influence these regions chemically. The induced pyrexia may assist in making chemotherapy more effective in this region.

In the second case it is of interest to observe that the chills ceased after the inauguration of the physically induced pyrexia. Following the fever treatments, the systemic temperature usually falls to a relatively low level from which it gradually reascends. We have observed this to occur also in cases of gonorrhea when our treatment has not been adequate to kill all the organisms. The induced fever of itself produces a leukocytosis.[6] This makes it of particular value in the treatment of leukopenia, which so frequently occurs after the ingestion of these drugs. Thus in one instance a white blood cell count of 4,950 was raised to 6,800 by a relatively mild pyrexia session.

In 1933 one of us applied physically induced pyrexia (without additional chemotherapy) to a patient suffering from subacute bacterial endocarditis. At the time the patient was actively embolizing. Following the second treatment, showers of numerous emboli caused an exitus. Postmortem examination showed the body organs to be filled with numerous fresh and old emboli. No deaths occurred as a result of the fever treatments in our present series of cases.

Krusen and Bennett[7] reported 6 cases unsuccessfully treated with sulfanilamide and hyperthermia. Ferderber,[8] applying this combined therapy to 3 patients, reports two recoveries. Solomon[9] has observed five apparent recoveries out of a series of 17 patients after a combination of sulfonamide and pyrexia induced by the intravenous injection of killed typhoid bacteria. In all reported series of cases treated with any of the sulfonamide drugs, with or without pyrexia, transient periods of apparent recovery may occur during which the temperature may remain low and the blood culture be negative. Unless the patients have remained well for many months or years, it is unwarranted to regard them as cured.

## CONCLUSION

Our experience would indicate that physically induced pyrexia enhances the value of chemotherapy in the treatment of subacute bacterial endocarditis. Of 2 cases reported, one was due to Streptococcus viridans and one to B. influenzae, in which recovery occurred and the patients have been well for two years and for ten months respectively. A third patient, with Streptococcus viridans endocarditis, has been well for four months, but this interval is still too brief to describe as a cure. In 13 cases the disease was influenced by the therapy only temporarily or not at all. These clinical results support the in vitro observations of White that the effectiveness of the sulfonamide drugs is materially enhanced at sustained higher elevations of temperature.

471 Park Avenue—110 East Eightieth Street.

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# Clinical Notes, Suggestions and New Instruments

## FATAL AGRANULOCYTOSIS FROM SULFATHIAZOLE

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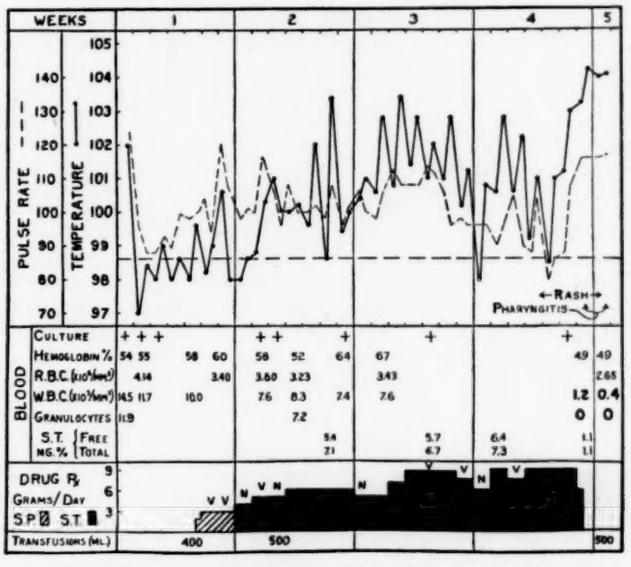
The chief objective in the search for new chemotherapeutic agents is to find drugs which have both greater effectiveness and lower toxicity. Sulfathiazole, according to some observers, presents a number of favorable features in these respects when compared with other sulfonamides that are in common use. One of the features usually mentioned is that acute agranulocytosis resulting from its use has not been reported.[1] We present here a case in which this complication occurred and proved fatal.

### REPORT OF CASE

*History.*—An American woman aged 38, a housewife, was admitted to the Boston City Hospital on June 23, 1940. She had been in good health until seven weeks previously, when she began to have drenching sweats at night and a spiking temperature reaching 103 to 104 F. daily, which continued to the time of entry. She had occasional chills during this time, and her physician kept her in bed. She lost 22 pounds (10 Kg.) up to the time of entry. For a few days she had suffered sharp, stabbing pain in the left side of the upper part of the abdomen (in the region of the spleen) and in the left side of the lower portion of the chest, both pains becoming worse on inspiration. Just before entry, her left shoulder and the upper part of her left arm became painful and she experienced some urgency of urination. She remembered vaguely having had a slightly swollen ankle during the previous winter but could recall no details. There was no other previous history of swollen or painful joints, rheumatic fever or cardiac symptoms. The patient had never been treated with sulfonamides before. She had one child, aged 9 years, who had suffered an injury at birth and was mentally retarded. Her past history, family history and marital history were otherwise irrelevant.

*Physical Examination.*—The patient was fairly well developed but thin and of small stature. At the time of admission she had no respiratory distress but complained of pain in the upper portion of her left arm and left shoulder on changing her position. The skin was pale, but warm and moist. The veins of the neck were slightly distended, and there were a few small, nontender cervical nodes on both sides. The heart was somewhat enlarged to the left, with the left border of dulness in the fifth intercostal space 11 cm. to the left of the midsternal line and the maximum impulse felt in the fourth intercostal space 8 cm. from the midsternal line. The heart sounds were regular and of good quality, the pulmonic second sound being sharp and metallic and much louder than the aortic second sound. There was a blowing systolic murmur and a low-pitched rumbling diastolic murmur at the apex, transmitted to the left axilla. A systolic murmur was also heard over the base of the heart and was loudest over the second interspace on the left side. The liver could be felt at the right costal margin on deep inspiration. There was definite clubbing of the fingers. The rest of the physical examination at this time gave negative results. In particular, no petechiae were seen, nodules were not felt, the joints were not swollen or tender, the lungs were entirely clear, the spleen was not felt, there was no edema of the extremities and the reflexes were normal and equal bilaterally, although slightly hyperactive.

*Laboratory Data.*—The most significant data are shown in the accompanying chart. Other relevant findings included the following: A catheterized specimen of urine on admission showed 1 to 2 red blood cells and 8 to 10 white blood cells with occasional clumps but no casts and negative reactions for sugar and albumin. Culture of this specimen of urine yielded enterococci and Staphylococcus aureus. Numerous subsequent specimens of urine showed either no albumin or the slightest trace, but no formed elements were seen on microscopic examination of the sediments. The blood smear on admission showed a differential leukocyte count of 82 per cent polymorphonuclear neutrophils, 16 per cent lymphocytes and 2 per cent monocytes; the red blood cells were slightly hypochromic and varied somewhat in size, and the platelets appeared normal. Subsequent differential leukocyte counts were essentially the same until July 20 and 21, when there were no granulocytes seen in the blood smears, only lymphocytes and rarely a monocyte. The blood nonprotein nitrogen level was 30 mg. per hundred cubic centimeters on admission and 49 mg. two days later. The blood Hinton reaction was negative. A roentgenogram of the chest showed the heart slightly enlarged to the right and left, the shape being consistent with mitral stenosis. There was slight mottling of both lung bases, interpreted as congestive changes. An electrocardiogram taken on the day after admission showed sinoauricular tachycardia; the PR interval was 0.16, with low voltage of QS complexes (0.6 millivolts); the T wave in leads 1 and 2 was low, in lead 3 inverted and in lead 4 diphasic; there was preponderance of the left ventricle. These findings are interpreted as consistent with myocardial disease.




A case of acute agranulocytosis resulting from sulfathiazole therapy. Blood culture + = positive for Streptococcus viridans; granulocytes = total number in thousands per cubic millimeter; S. T. = sulfathiazole; S. P. = sulfapyridine; N = nausea; V = vomiting. Only the doses of drugs actually taken by the patient are charted.

*Hospital Course and Treatment* (see chart).—With the history and the results of physical examinations and with reports of Streptococcus viridans in repeated blood cultures, a diagnosis was made of subacute bacterial endocarditis superimposed on rheumatic heart disease with mitral stenosis. On the fifth day in the hospital, treatment with sulfapyridine (1 Gm. every four hours) was started, but because of the severe nausea and vomiting sulfathiazole was substituted and given at first in the same dosage and, beginning in the middle of the third week, in 1.5 Gm. amounts every four hours. A number of doses were refused from time to time by the patient, and the nausea and vomiting continued intermittently. Her appetite remained poor throughout, but she maintained a good intake of fluids. The patient was also given three transfusions, as noted in the chart. The first of these was followed by a chill of moderate severity and by a brief period of pulmonary congestion and edema which improved after the application of tourniquets to the extremities and the administration of oxygen and small doses of morphine. On the tenth day, a few petechiae were noted below the angles of the scapulas and on the second finger of the right hand. On the nineteenth day, there was tenderness in the region of the spleen and a friction rub was heard over it. At that time there was also a shower of petechiae seen over the left breast.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), and the Mallory Institute of Pathology, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. The literature concerning sulfathiazole has recently been reviewed by Spink, W. W., and Hansen, A. E.: Sulfathiazole: Clinical Evaluation, J. A. M. A. **115**: 840-847 (Sept. 7) 1940.

The course of the temperature, pulse rate and blood content is shown in the chart. On the twenty-fifth day a few small papules appeared on the forearms. These increased slowly in size and number on both forearms and elbows, and a few faintly red, tender subcutaneous nodules 5 to 10 mm. in diameter appeared three days later on the knees and anterior surfaces of the lower legs. On the twenty-eighth hospital day, after several days when blood counts had not been done, the leukocyte count was found to be 1,200 and no granulocytes were seen in the smear. Sulfathiazole therapy was stopped as soon as this was learned, and the patient was given a blood transfusion, 10 cc. of liver extract and 30 cc. of pentnucleotide intramuscularly, and an additional 1,500 cc. of physiologic solution of sodium chloride intravenously. The throat at this time showed a few pus-filled crypts in the right tonsil, and later ulcerations on the tonsils, which increased without any marked surrounding inflammatory reaction. Numerous small petechiae also appeared on the trunk. The next day, while the patient was apparently sleeping peacefully, she suddenly gasped and died.

The clinical diagnoses were subacute bacterial endocarditis (Streptococcus viridans) of the mitral valve; splenic infarct; rheumatic heart disease with cardiac enlargement, mitral stenosis and regurgitation; acute agranulocytosis due to sulfathiazole; sulfathiazole dermatitis, and secondary hypochromic anemia.

*Significant Observations at Autopsy.*[2]—The body weight was 36.5 Kg. The head was not examined. The heart weighed 260 Gm. and had three endocardial vegetations: the largest was on the left auricle, measured 1 cm. in its greatest diameter, and was composed of a firm, gray thrombus attached to an underlying cluster of tiny (1 mm.) elevations; the second, almost the same size, was located on the aortic leaflet of the mitral area, and the third was smaller and was located on the other mitral leaflet, the latter two being covered by a soft red blood clot. The chordae tendineae of the mitral valve were slightly thickened. The aortic valve was not appreciably changed. Cultures of the heart's blood and vegetations yielded Str. viridans. Microscopically, sections of the myocardium showed several moderately large areas in which the muscle fibers were replaced by areas infiltrated with lymphocytes and macrophages. The vegetations consisted mainly of fibroblasts with an interstitial infiltration of lymphocytes and macrophages, many of the latter being swollen or joined together to form giant cells. The outer edge of each vegetation was irregular and covered by masses of fibrin, erythrocytes and a few macrophages. An occasional cluster of gram-positive coccus-like bodies was found in the Gram-Weigert stained sections. No polymorphonuclear cells were present either in the vegetations or in the overlying blood clot.

The spleen weighed 220 Gm. and had three typical gray and moderately firm infarcts, one about 3.5 cm. and the other two about 1 cm. in greatest dimension. Histologically, these were large areas of infarct necrosis with surrounding zones of granulation tissue. On the capsular and cut surfaces of each renal cortex there were scattered red punctate lesions, but there were no gross infarcts. On microscopic examination an occasional glomerulus was found with a well formed crescent. There were interstitial collections of lymphocytes and plasma cells, and one subcapsular area contained engorged capillaries, extravasated blood and lymphocytic infiltration. No polymorphonuclear leukocytes were seen in any of the sections. There were a few petechiae along the gastrointestinal tract. In the lungs, the alveolar walls were congested. There were also lymphocytes and plasma cells and a few macrophages but no polymorphonuclear leukocytes either in the alveolar walls or within their lumens.

The femoral and vertebral bone marrow was grayish red and soft. Microscopically, the vertebral marrow showed an absence of maturation of the white blood cells. There was a moderately increased number of stem cells but only a few myelocytes and no adult polymorphonuclear neutrophils or eosinophils. Megakaryocytes were abundant, and the cells of the erythrocyte series were present in normal numbers. The femoral marrow was hyperplastic, but arrest of maturation of the white blood cells was present there also. There were many stem cells, a few myelocytes, several megakaryocytes and areas of erythrocyte production but no adult polymorphonuclear cells.

The anatomic diagnoses were acute agranulocytosis; bacterial endocarditis involving the left auricular endocardium and mitral valve (Str. viridans); old rheumatic endocarditis of the mitral valve; splenic infarct, organizing; focal embolic glomerulonephritis and focal interstitial nephritis; pulmonary congestion (moderate), and petechial hemorrhages of the skin and gastrointestinal tract.

2. Autopsy was performed by Drs. J. B. Hamblet and P. C. Kennedy and the findings reviewed by Dr. Frederic Parker Jr.

### COMMENT

The clinical and pathologic pictures are characteristic of subacute bacterial endocarditis and acute agranulocytosis. The latter apparently began during the end of the third week of treatment with sulfathiazole. No other drugs known to produce this condition were used after treatment with sulfathiazole was begun, although sulfapyridine had been given for two days previously. No past history of treatment with sulfonamide drugs could be elicited. The exact cause or mechanism of the sudden death in this case is not certain. The appearance of the characteristic though mild rash, followed shortly by high fever and complete absence of granulocytes and a marked drop in the other leukocytic elements of the peripheral blood, leaves little doubt that we were dealing with acute agranulocytosis resulting from sulfathiazole therapy and that this was the determining factor in the fatal outcome.

In the present case, death from the underlying endocarditis was inevitable, but it might have been postponed had the leukopenia been recognized earlier and chemotherapy been stopped promptly thereafter. The events in this case serve to emphasize the importance of close observation of the blood in patients who are under prolonged therapy with sulfonamides. New related chemicals may be used in large numbers of cases before such serious complications are encountered. The early favorable experiences may result in excessive confidence and, in turn, in a relaxation of necessary and persistent care.

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## RECURRENT PNEUMOCOCCIC MENINGITIS TREATED WITH SULFAPYRIDINE

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In 1938 Whitby [1] demonstrated the effectiveness of sulfapyridine against pneumococcic infections in mice. A number of favorable reports [2] have appeared which indicate that this drug has pronounced therapeutic value in the treatment of pneumococcic meningitis. During the past months Hodes and his associates [3] have used sulfapyridine and its sodium salt in 17 cases, with 47 per cent recovery. Recently Kolmer [4] presented a comprehensive review of sulfapyridine therapy in pneumococcic meningitis and discussed its therapeutic value.

We are presenting a patient with recurrent pneumococcic meningitis who was treated with sulfapyridine in each episode. The sulfapyridine concentrations of the blood and spinal fluid were of peculiar significance.

From the Departments of Medicine and Biochemistry, Medical College of Virginia.

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2. These reports include:
Reid, G. C. K., and Dyke, S. C.: Pneumococcal Meningitis Treated with M. & B. 693: Recovery, Lancet **2**: 619 (Sept. 10) 1938.
Robertson, Kenneth: Case of Pneumococcal Meningitis Treated with M. & B. 693, ibid. **2**: 728 (Sept. 24) 1938.
McAlpine, Douglas and Thomas, G. C.: Pneumococcal Meningitis Treated with M. & B. 693, ibid. **1**: 754 (April 1) 1939.
MacKeith, R. C., and Oppenheimer, G.: Pneumococcal Meningitis: Report of Five Consecutive Cases Treated with Sulfanilamide-Pyridine (M. & B. 693), ibid. **1**: 1099 (May 13) 1939.
May, Kenneth: A Fatal Case of Pneumococcal Meningitis Treated with M. & B. 693, ibid. **1**: 1100 (May 13) 1939.
Raman, P. S.: Pneumococcal Meningitis Treated with M. & B. 693, ibid. **1**: 1101 (May 13) 1939.
Backhouse, T. C., cited by Ross, R. W.: Acquired Tolerance of Pneumococcus to M. & B. 693, ibid. **1**: 1207 (May 27) 1939.
Barnett, H. L.; Hartmann, A. F.; Perley, A. M., and Ruhoff, M. B.: The Treatment of Pneumococcic Infections in Infants and Children with Sulfapyridine, J. A. M. A. **112**: 518 (Feb. 11) 1939.
Cunningham.[5]

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REPORT OF CASE

*First Admission.*—L. R., a Negro woman aged 32, was admitted to St. Philip Hospital (Negro division of the Medical College of Virginia hospitals) Dec. 15, 1939 and discharged apparently well December 31. Her history revealed that she had been well until the day before admission, when malaise and a severe frontal headache developed. She vomited once and later that night became irrational and stuporous.

Examination on admission revealed that the patient was obese and was in a disoriented condition; she could be aroused sufficiently to complain of a severe headache. There was marked nuchal rigidity. The blood pressure was 115 systolic and 50 diastolic. The heart was normal except for an insignificant apical systolic murmur and an occasional ectopic beat. Otherwise physical examination was negative except that the Kernig sign was present on both sides.

The urine had a specific gravity of 1.013, with albumin (2 plus), but showed no sugar or sediment. The temperature was 102 F., the pulse rate 80 and the respiratory rate 28. The blood showed hemoglobin 68 per cent, erythrocytes 3,870,000 and leukocytes 25,100 with 89 per cent polymorphonuclear neutrophils. The blood sugar level was 102 mg. per hundred cubic centimeters and the nonprotein nitrogen level 29 mg. per hundred cubic centimeters. The Kline test gave negative results. The spinal fluid pressure was 250 mm. of water. The fluid was cloudy and contained 8,000 cells per cubic millimeter, with 98 per cent polymorphonuclear neutrophils; pneumococcus type XVII was isolated from the spinal fluid.

The patient was first treated with sulfanilamide; an initial dose of 60 grains (4 Gm.) was given followed by 20 grains (1.3 Gm.) every four hours. Sulfanilamide was used until the causative organism was identified and then sulfapyridine in therapeutic doses was substituted. The drug was continued from December 16 to 27; clinical improvement with a normal temperature resulted on December 18.

The spinal fluid was normal on December 20 and the white blood cell count was 7,750. Sulfapyridine values of the blood and spinal fluid are given in the accompanying table.

*Second Admission.*—The patient was readmitted Jan. 24, 1940 and discharged apparently well Feb. 24. Her history in the interval was that she had been well after her discharge from the hospital until two days before readmission. At this time, January 22, she suffered headache, pain and stiffness of the neck. On the morning of admission her headache became severe; she had a chill and vomited.

The patient was rational; examination showed marked nuchal rigidity and the presence of Kernig's and Brudzinski's sign. The temperature was 103 F., pulse rate 120 and respiratory rate 26. The rest of the examination was not significant.

The urine was normal. The blood showed hemoglobin 68 per cent, erythrocytes 3,180,000 and leukocytes 11,700 with 79 per cent polymorphonuclear neutrophils. The spinal fluid was cloudy and the smear and culture were sterile.

The patient was treated with 60 grains (4 Gm.) of sulfapyridine on admission and 15 grains (1 Gm.) every four hours day and night from January 24 to February 1, then 15 grains every six hours until February 18 and then 7½ grains (0.5 Gm.) every six hours until her discharge from the hospital. Her temperature fell to normal twenty-four hours after sulfapyridine administration had been begun and remained so during her stay at the hospital. Because of lack of cooperation of the patient we were able to obtain only the one sample of spinal fluid. Examination, including roentgenograms, of the mastoids and paranasal sinuses, was negative for any focus of infection. She was discharged symptom free February 24 and did not report to the clinic as directed.

*Third Admission.*—She was readmitted for the third time on June 2 and discharged June 17, apparently recovered. The intervening history was that she had been well until the day before admission, at which time she awoke with a severe headache and vomited once. Later she became irrational and had a severe chill. Then she became stuporous and remained in this condition until she was readmitted.

On examination the patient was well developed and well nourished but was stuporous, with marked nuchal rigidity. Both the heart and the lungs were normal. Kernig's sign was present on both sides.

The urine was normal, and the blood studies showed 84 per cent hemoglobin, 4,160,000 erythrocytes and 23,900 leukocytes, with 85 per cent polymorphonuclear neutrophils. The spinal fluid was cloudy, and the pressure was 600 mm. of water; the leukocyte count was 45,000 with 82 per cent polymorphonuclear neutrophils. Pneumococcus type XXVIII was isolated from the spinal fluid.

Sulfapyridine was again administered in an initial dose of 60 grains and 15 grains every four hours. Recovery was prompt, and a normal temperature was present by June 5. Again the sulfapyridine levels of the blood and spinal fluid were determined; the blood level was 11.4 mg. and the spinal fluid level 26.2 mg. per hundred cubic centimeters on June 4.

*Fourth Admission.*—The patient was admitted for the fourth time October 16. Her history in the interval revealed that she had felt well and had continued working (at a tobacco factory) until the morning of this admission, when she suffered malaise, severe headache, aching over the body and pain and stiffness of the neck and back. She vomited several times; she also had a chill followed by fever. In the four month interval between her last discharge from the hospital in June and this admission she had noticed clear fluid dripping from her nose from time to time.

The patient was acutely ill, febrile and drowsy but could be aroused. She complained of headache and stiffness of the neck. There was no discharge from the nose. There was marked nuchal rigidity. Kernig's sign was absent. The remainder of the physical examination was negative except for diminished breath sounds and a few fine rales in the base of the left lung. The blood pressure was 110 systolic and 60 diastolic. The temperature was 104 F., the pulse rate 140 and the respiratory rate 40.

*Sulfapyridine Values of Blood and Spinal Fluid*

| Date | Blood Level, Mg. per 100 Cc. | Spinal Fluid Level, Mg. per 100 Cc. |
|---|---|---|
| December 18 | 9.2 | 22.4 |
| December 20 | 12.3 | 48.0 |
| December 23 | 9.2 | 6.1 |
| December 29 | 8.0 | 1.0 |

Lumbar puncture was performed; the fluid had a ground-glass appearance and was under a pressure of 250 mm. of water. Smear and culture of the spinal fluid failed to show the presence of any organism. The white cell count of the spinal fluid was 6,400 cells per cubic millimeter, with 80 per cent polymorphonuclear neutrophils. The protein content of the spinal fluid was over 100 mg. per hundred cubic centimeters.

Urinalysis was negative. The blood showed leukocytes 6,400 with 59 per cent polymorphonuclear neutrophils, erythrocytes 4,400,000 and hemoglobin 80 per cent. Blood sugar and nonprotein nitrogen levels were normal.

Culture of the blood was negative for bacteria.

A roentgenogram taken with a portable apparatus confirmed the clinical diagnosis of bronchopneumonia in the lower lobe of the left lung. No sputum could be obtained. Culture of material from the nose showed no pneumococci.

The patient was treated with sulfapyridine as previously, 60 grains being given as the initial dose and 15 grains every four hours for six days and then 15 grains every six hours for eight more days, and then administration of the drug was discontinued. Her hemoglobin content and white blood cell count were observed during treatment, and neither showed a decrease.

The patient's clinical improvement was rapid. Her temperature fell to 100 F. in twenty-four hours and to normal in three days. It remained normal during the remainder of her stay in the hospital. Her spinal fluid cell count was 41 to the cubic millimeter, of which only 5 were polymorphonuclear neutrophils, on the fourth day.

Quantitative determinations of the sulfapyridine content of the blood and spinal fluid were made four days after the beginning of the administration of the drug. Unlike the values

obtained during the patient's first and third admissions, the blood sulfapyridine level was higher than the spinal fluid sulfapyridine level. The blood sulfapyridine level was 9.4 mg., and the spinal fluid sulfapyridine level was 7.1 mg. per hundred cubic centimeters.

Roentgen studies of the skull and paranasal sinuses failed to reveal any evidence of a basal fracture or of any abnormality of the sinuses or mastoids.

### COMMENT

We have presented a patient who has had suppurative meningitis four times within one year. On admission pneumococcus type XVII was isolated by culture from the spinal fluid. On the second admission the spinal fluid was sterile. On the third admission pneumococcus type XXVIII was isolated by culture from the spinal fluid and on the fourth admission the spinal fluid was again sterile. We cannot say whether the patient had four separate infections or whether the last three attacks were flare-ups from a dormant focus from the first infection. As far as we have been able to determine, there have been no cases of recurrent pneumococcic meningitis reported; this is probably due to the high mortality of this disease before the sulfapyridine era. Previous to the use of sulfapyridine, nearly all patients died before they could recover and suffer recurrences.

The recurrence of meningococcic meningitis is well known.[5] It may be due to infection of the paranasal sinuses or to small residual collections of pus within the meninges the breakdown of which causes a recurrence of the meningitis. Were it not for the fact that pneumococcus type XVII was isolated once, and later pneumococcus type XXVIII was isolated, we would feel that the "recurrence" was the result of encapsulated foci in the meninges. However, there is still a possibility of a transformation of the type of pneumococcus.

We regret that we could not study further the sulfapyridine levels of the spinal fluid, but each time the patient improved she fought any attempts at lumbar puncture, and we did not feel that it was safe to restrain her and perform the puncture under force.

The chemical examination of the blood and spinal fluid for free sulfapyridine according to Marshall's method[6] presented a rather interesting observation. In a previous case of pneumococcic meningitis we had demonstrated a blood value of less than one third of the spinal fluid value. This case led us to investigate like cases without a duplication of any such results, with the exception of the case just presented. During the past ten months we have analyzed the blood and spinal fluid of 8 patients and observed this in 2 of them.

Previously Cutts and his associates[7] reported the blood values higher in 1 case and Cunningham[8] made a similar observation in 1 case. Of the 17 patients of Hodes,[3] only 9 had comparable values, and in no case was the sulfapyridine concentration higher in the spinal fluid than in the blood. Our patient's spinal fluid values were higher than her blood values on her first and third admissions, but on her last admission her blood level was higher than the spinal fluid value. However, at the last admission the sulfapyridine concentration in the spinal fluid was 7.1 mg. per hundred cubic centimeters, which is above the usual level found in patients under treatment with the drug.

### SUMMARY

The patient here presented was admitted to the hospital four times within a year with suppurative meningitis. Twice a pneumococcus, each time of a different type, was isolated from the spinal fluid. The other times the spinal fluid showed no organisms on smear or culture. On each occasion sulfapyridine therapy was effectual.

On two admissions, the sulfapyridine concentration in the spinal fluid was greater than that in the blood. On the last admission the blood concentration was greater than the spinal fluid level.

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## USE OF SULFATHIAZOLE IN STAPHYLOCOCCIC MENINGITIS WITH RECOVERY

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The seriousness of staphylococcic meningitis is well known, and only scattered reports of recovery from this condition, numbering less than a dozen, have appeared in the literature. The methods of treatment have consisted of simple cisternal drainage,[1] bacteriophage therapy,[2] administration of gentian violet,[3] sulfanilamide (or azosulfamide) therapy,[4] or combinations of these methods. Recently Dietel and Kaiser[5] made note of the recovery of a child with staphylococcic meningitis following therapy with sulfathiazole.

Sulfathiazole, synthesized by Fosbinder and Walter[6] and Lott and Bergeim[7] has attracted attention in the clinical treatment of staphylococcic infections[8] and its efficacy against the staphylococcus has been attested experimentally by in vivo[9] and in vitro[10] methods.

It has been recently shown[11] in this clinic, however, that sulfathiazole, unlike the other sulfonamide derivatives, does not readily diffuse into the noninflammatory cerebrospinal fluid. This finding immediately suggested the possible inefficacy of sulfathiazole in the treatment of meningeal infections and made evident the necessity for careful observation of the use of this drug in meningitis.

The present case is reported, first, to demonstrate that sulfathiazole does not readily diffuse into a purulent cerebrospinal fluid; second, to present evidence that an adequate concentration

The sulfathiazole used in this case was obtained through the courtesy of Dr. George A. Harrop, Squibb Institute for Medical Research, New Brunswick, N. J.

From the Departments of Internal Medicine and Surgery, Yale University School of Medicine, and the Medical and Surgical Services of the New Haven Hospital.

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of sulfathiazole in the spinal fluid can be maintained by the intrathecal administration of a 0.5 per cent solution of sodium sulfathiazole in saline solution, and, third, to record the recovery of a case of Staphylococcus aureus meningitis treated by oral, parenteral and intrathecal therapy with sulfathiazole. This recovery is the only one which has occurred in 11 cases of staphylococcic meningitis observed at the New Haven Hospital during the past twelve years, despite varied types of therapy.

## REPORT OF CASE

*History.*—M. B., a man aged 40, an Italian, was admitted to the Neurological Unit of the Surgical Service (under the direction of Dr. William J. German) of the New Haven Hospital, July 3, 1940, because of jacksonian convulsions on the left side. The history, physical examination and ventriculography demonstrated the presence of a space-occupying tumor in the right parietal region. On July 10 a right central craniotomy was performed by one of us (A. E. N.) with removal of a fibrillary astrocytoma situated in the right precentral leg area. Ventricular fluid removed at this time was crystal clear and contained 22.5 mg. of protein per hundred cubic centimeters.

The immediate postoperative course was moderately febrile, but the temperature approached normal limits by July 14. On July 16 a small amount of bloody fluid was aspirated from under the incision in the scalp. Because of increasing restlessness, lumbar puncture was done July 17 and 20 cc. of a crystal clear fluid under 260 mm. of water pressure was removed, apparently affording some degree of relief. Culture taken of this fluid remained sterile. On the following day (July 18) the patient complained of headache and a slightly stiff neck. The Kernig sign was equivocally present. There was a small amount of blood-tinged fluid draining from the craniotomy wound which on culture yielded a heavy growth of hemolytic Staphylococcus aureus. The temperature reached 102.8 F. that night and the patient became drowsy.

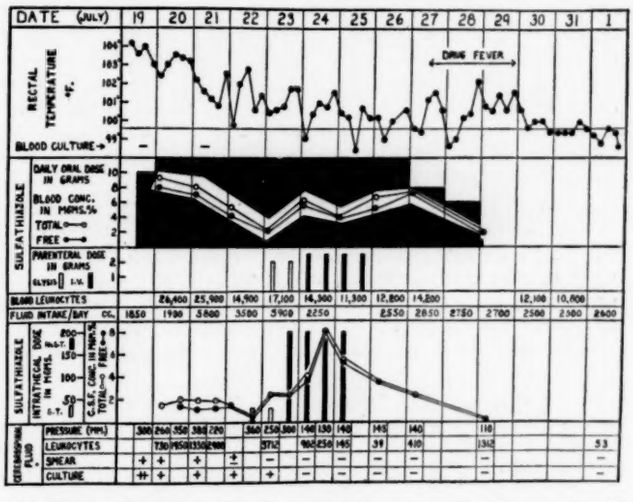
On the following day (July 19) the patient was irrational and semicomatose and signs of meningitis were definite, with stiff neck and the Kernig sign present bilaterally. The temperature was 104.2 F. A creamy, purulent, light red pus oozed copiously from the craniotomy wound. Lumbar puncture revealed the presence of cloudy cerebrospinal fluid under a pressure of 300 mm. of water. Smear of this fluid revealed the presence of gram-positive cocci, and on culture a moderate growth of hemolytic Staphylococcus aureus was obtained. Treatment with sulfathiazole was instituted the same afternoon, the patient receiving an initial dose of 4 Gm. by mouth, followed by 2 Gm. every four hours thereafter. On July 20 free drainage of the craniotomy wound was instituted by spreading the incision apart with a clamp and inserting two drains.

No definite improvement was noted during the next seventy-two hours, although drainage from the wound decreased and the patient appeared, perhaps, to be somewhat more conscious. On the other hand, the stiffness of the neck increased, both smear and culture of the spinal fluid remained positive for staphylococci, and the cellular elements of the cerebrospinal fluid, 95 per cent of which were polymorphonuclear leukocytes, steadily rose.

Since the sulfathiazole concentration[12] in the spinal fluid remained low in spite of an adequate concentration in the blood, it was thought advisable to begin intrathecal therapy with the drug. Accordingly, 30 cc. of a 0.1 per cent solution of sulfathiazole in physiologic solution of sodium chloride was administered intrathecally on July 22 and 23 following the drainage of 35 cc. of spinal fluid each time. Despite this procedure, the culture remained positive and the drug concentration rose but slightly. Hence, beginning July 23, the intrathecal administration of 40 cc. of 0.5 per cent sodium sulfathiazole in physiologic solution of sodium chloride was carried out twice a day in a manner similar to that already described. This procedure was sufficient to raise the sulfathiazole concentration in the cerebrospinal fluid to therapeutically satisfactory levels as demonstrated in the accompanying chart.

Coincident with these events, the sulfathiazole concentration in the blood steadily dropped to a low level of 2.2 mg. per hundred cubic centimeters, despite the continued daily oral administration of 12 Gm. of sulfathiazole, perhaps in part because of the high fluid intake. An attempt was made to raise the blood concentration of the drug by the subcutaneous administration of 2 Gm. of sulfathiazole twice a day in addition to the ingestion by mouth of 12 Gm. of the drug. However, this form of parenteral therapy was not satisfactory because of the inordinately large quantities of saline solution required when the drug is administered by hypodermoclysis. The problem of maintaining therapeutically satisfactory blood concentration of sulfathiazole was eventually solved by the injection intravenously of a 1 per cent solution of the sodium salt of the drug in physiologic solution of sodium chloride, the precautions recommended by Marshall and Long[13] being observed. In addition to this, the patient continued to receive 12 Gm. of sulfathiazole a day by mouth.

Improvement following the intrathecal and intravenous administration of the sodium salt of the drug was striking. The patient became rational and alert, stiffness of the neck steadily decreased, and drainage of the craniotomy wound practically ceased. Return of function to the left side of the body was rapid, and the temperature continued to fall by lysis. In addition, the leukocyte count in both blood and cerebrospinal fluid dropped toward normal and culture of the cerebro-




Laboratory data of patient with staphylococcic meningitis treated with sulfathiazole: *clysis*, sulfathiazole given by hypodermoclysis; *I. V.*, sodium sulfathiazole administered intravenously; *NaST*, sodium sulfathiazole; *S. T.*, sulfathiazole; and *C. S. F.*, cerebrospinal fluid.

spinal fluid became sterile and remained so after the first intrathecal administration of sodium sulfathiazole. Details of these findings are given in the chart.

On the ninth day of sulfathiazole therapy the temperature began to rise, reaching 102 F. on July 28. Though no cutaneous eruption appeared, the most likely explanation of this fever appeared to be that of "drug fever." Consequently sulfathiazole was discontinued, with a resultant drop of the temperature to normal.

Improvement continued at a steady pace; the patient remained afebrile and was discharged from the hospital in good condition on August 10.

The rise of the leukocyte count in the cerebrospinal fluid to 410 per cubic millimeter on July 27 and to 1,312 on July 29 was due to the presence of large numbers of swollen and degenerated polymorphonuclear cells. In a final lumbar puncture, done on August 1, the spinal fluid was clear and contained 53 cells per cubic millimeter, all of which were mononuclear cells.

*Bacteriology.*—The organism isolated from the cerebrospinal fluid was a small gram-positive coccus occurring in smear in small clumps and growing on agar in small, glistening, convex colonies containing a faint golden pigment. On defibrinated rabbit's blood agar plates, both in pour and in streaked plates,

12. The chemical analyses in this report were performed by Miss Janet M. Grubb.

13. Marshall, E. K., and Long, P. H.: Intravenous Use of Sodium Sulfapyridine, J. A. M. A. **112**: 1671 (April 29) 1939.

the colony was surrounded by a small zone (1 mm.) of complete hemolysis. The latter in turn was surrounded by a band of incomplete hemolysis ranging from 1 to 3 mm. in width, depending on the size of the colony and its position with respect to the surface of the agar. Mannite, lactose, dextrose, sucrose and maltose were fermented with the production only of acid. The coagulase test gave positive results.

### COMMENT

Comment has previously been made on the failure of sulfathiazole to diffuse into noninflammatory spinal fluid in satisfactory concentration, as contrasted with the ready diffusion of sulfanilamide and sulfapyridine. That this failure is true also to a certain degree in the case of purulent fluids has recently been demonstrated by Spink and Hansen [14] in cases of pneumococcic meningitis. The present case confirms their observations.

The reason for this difference in diffusion into the cerebrospinal fluid between sulfathiazole and other compounds of the sulfonamide series is not clear at the present time. It should be pointed out that the finding of an unduly high concentration in the spinal fluid of any of the sulfonamide drugs should be interpreted with caution if procaine hydrochloride has been used, for, as Long and Wood [15] have pointed out, contamination of the fluid by procaine hydrochloride yields erroneously high results by virtue of the fact that the free amino groups in procaine hydrochloride combine with the coupling reagent to give an intense violet color. Therefore certain precautions must be taken in securing samples of spinal fluid as well as other types of body fluid for chemical analysis. In this clinic we have ordinarily preferred to dispense with procaine hydrochloride and use an ethyl chloride spray.

As soon as the inadequate diffusion of sulfathiazole into the cerebrospinal fluid in this case was known, it became evident that the oral use of this drug alone might not be satisfactory in the treatment of the meningitis. To date, no clinical report except that of Dietel and Kaiser [5] has appeared to confirm or contradict this possibility. Spink and Hansen [14] have treated three patients with pneumococcic meningitis with sulfathiazole but their report does not allow evaluation of the effect of sulfathiazole alone, since antiserum was used both parenterally and intrathecally.

That the use intrathecally of a 0.1 per cent solution of sulfathiazole in saline solution, which is about the limit of solubility of this drug at room temperature, may not be satisfactory, at least in staphylococcic meningitis, is apparent if one may judge from the absence of the obvious therapeutic effect in the present case. It is well known that more concentrated solutions of sulfathiazole may readily be made by the use of its sodium salt, but the high alkalinity of the 5 per cent solution commonly used for intravenous treatment might be expected to have a deleterious effect on the spinal cord. However, in view of the well-nigh fatal prognosis in cases of staphylococcic meningitis, we believed that the use of a 0.5 per cent solution of sodium sulfathiazole in saline solution should be tried as a last resort, after persistence of positive spinal fluid cultures and an increase in the symptoms of meningitis had occurred. The subsequent clinical improvement and disappearance of staphylococci from cultures of the spinal fluid would appear to have warranted the trial and speaks for the efficacy of this method of therapy.

Although this patient shows to date (Oct. 15, 1940) no evidence of damage to the central or peripheral nervous system that can be attributed to the drug, the possibility of injury to the spinal cord, even by a 0.5 per cent solution of sodium sulfathiazole, cannot be dismissed. Consequently, a further investigation of this problem is being undertaken.

The fact that on the same daily dosage there may be considerable variation in the blood concentration of sulfathiazole from patient to patient has been demonstrated.[11] The present case illustrates the fact that there may be a similar variation from day to day in the same patient and emphasizes the need for daily determinations of the blood concentration of sulfathiazole in critically ill patients, with immediate resort to parenteral treatments if adequate blood concentration is not maintained by oral therapy alone. The administration of sulfathiazole by hypodermoclysis is ordinarily unsatisfactory, since the low solubility of the drug at room temperature necessitates the administration of excessively large quantities of saline solution. Therefore it may, under certain circumstances, be preferable to employ solutions of the sodium salt intravenously. Ordinarily a 5 per cent solution of sodium sulfathiazole in sterile distilled water is given intravenously, following the directions of Marshall and Long [13] in preparation of the solution. At times, to fortify oral therapy, we have used a 1 per cent solution of sodium sulfathiazole in physiologic solution of sodium chloride given intravenously, and this proved adequate in the case reported here.

### SUMMARY

1. In the case of Staphylococcus aureus meningitis reported, recovery occurred following sulfathiazole therapy.

2. Despite an adequate concentration in the blood, diffusion of sulfathiazole into the cerebrospinal fluid was unsatisfactory.

3. It was necessary to use a 0.5 per cent solution of sodium sulfathiazole intrathecally before sterilization of the spinal fluid was obtained. No ill effect from this solution could be demonstrated.

4. In order to maintain the blood concentration of sulfathiazole at a satisfactory level, the use of the sodium salt of the drug intravenously was necessary, despite dosage of 12 Gm. a day by mouth.

14. Spink, W. W., and Hansen, A. E.: Sulfathiazole: Clinical Evaluation, J. A. M. A. **115**: 840 (Sept. 7) 1940.

15. Long, P. H., and Wood, W. B.: Observations upon the Experimental and Clinical Use of Sulfapyridine: II. The Treatment of Pneumococcal Pneumonia with Sulfapyridine, Arch. Int. Med. **13**: 487 (Sept.) 1939.

## RENAL COMPLICATIONS DUE TO SULFATHIAZOLE

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Urinary complications due to sulfathiazole have been described in animals [1] and in man.[2] At the Cleveland City Hospital, of fifty-four patients with pneumonia treated with sulfathiazole,[3] thirty-three (61.1 per cent) had crystals of the drug in the urine. In a control series of fifty-six patients treated with sulfapyridine, sixteen (28.6 per cent) had crystals in the urine. This difference is statistically highly significant.[4]

Sulfathiazole crystals appear in the urine more often than sulfapyridine probably because sulfathiazole is excreted more rapidly and hence a greater amount of the drug has to be administered in order to maintain a satisfactory concentration in the blood. In the cases under consideration an average dose of 52.4 Gm. of sulfathiazole administered over an average period

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1. The experiments on animals include:
Van Dyke, H. B.; Greep, R. O.; Rake, Geoffrey, and McKee, Clara M.: Observations on the Toxicology of Sulfathiazole and Sulfapyridine, Proc. Soc. Exper. Biol. & Med. **42**: 410 (Nov.) 1939.
Cooper, F. B.; Gross, Paul, and Lewis, Marion: Chemotherapeutic Evaluation of Sulfanilamide Derivatives of Heterocyclic Amines, Proc. Soc. Exper. Biol. & Med. **42**: 421 (Nov.) 1939.
Gross, Paul; Cooper, F. B., and Scott, R. E.: Urolithiasis Medicamentosa, Urol. & Cutan. Rev. **44**: 205 (April) 1940.
Toomey, J. A.: Personal communication to the author.

2. The work on man includes:
Reinhold, J. G.; Flippin, H. F., and Schwartz, Leon: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man, Am. J. M. Sc. **199**: 393 (March) 1940.
Long, P. H.: Thiazole Derivatives of Sulfanilamide, J. A. M. A. **114**: 870 (March 9) 1940.
Flippin, H. F.; Schwartz, Leon, and Rose, S. B.: The Comparative Effectiveness and Toxicity of Sulfathiazole and Sulfapyridine in Pneumococcic Pneumonia, Ann. Int. Med. **13**: 2038 (May) 1940.
Knoll, A. F., and Cooper, F. B.: Clinical Urolithiasis Medicamentosa Due to Sulfathiazole, Urol. & Cutan. Rev. **44**: 292 (May) 1940.
Arnett, J. H.: Hematuria from Sulfathiazole Therapy in Pneumonia, J. A. M. A. **115**: 362 (Aug. 3) 1940.
Pepper, D. S., and Horack, H. M.: Crystalline Concretions in the Renal Tubules Following Sulfathiazole Therapy: Widely Patent Foramen Ovale in a Patient Aged 77, Am. J. M. Sc. **199**: 674 (May) 1940.
Long, P. H.; Haviland, J. W.; Edwards, Lydia B., and Bliss, Eleanor A.: The Toxic Manifestations of Sulfanilamide and Its Derivatives, J. A. M. A. **115**: 364 (Aug. 3) 1940.
Allott, E. N.: Clinical Experiences with Sulfathiazole, Brit. M. J. **1**: 1033 (June 22) 1940.

3. Sulfathiazole was available for study through cooperation with the Squibb Institute for Medical Research and the Medical Research Division of the Winthrop Chemical Company.

4. In this article the term "significant" refers to a difference which could be produced by chance in less than 5 per cent of trials as demonstrated by application of the chi square test; "highly significant" refers to a difference so great that it could be produced by chance in less than 1 per cent of trials, again as demonstrated by application of the chi square test.

of 5.2 days produced an average blood concentration of 5.8 mg. per hundred cubic centimeters of the free drug in the blood. In the cases treated with sulfapyridine, an average total dose of 34.4 Gm. given over an average period of 6.8 days resulted in an average blood concentration of 5.4 mg. per hundred cubic centimeters. In short, it took 10.1 Gm. of sulfathiazole a day in contrast to 5.1 Gm. of sulfapyridine to produce a blood level of from 5 to 6 mg. per hundred cubic centimeters.

Hematuria was found microscopically in eight cases in the sulfathiazole treated group (14.8 per cent) and in six in the sulfapyridine group (10.7 per cent), a difference which is not statistically significant. In most of the patients the hematuria was of no consequence. Two cases in the sulfathiazole treated group, however, were unusual:

### REPORT OF CASES

CASE 1.—A. D., a white man aged 65, entered the Cleveland City Hospital at 5:30 p. m. March 22, 1940, with type I pneumococcus pneumonia and received sulfathiazole. The dosage was 4 Gm. by mouth repeated in four hours, followed by 2 Gm. every four hours. The temperature became normal in thirty hours and improvement was definite.

On March 24, 25 and 26 the blood level of sulfathiazole was 6.8, 5.0, and 4.9 mg. per hundred cubic centimeters respectively. The urine, normal on March 23, showed crystals on the 24th and 25th and many crystals and a few red blood cells microscopically on the 26th. The administration of the drug was discontinued at once, a total of 48 Gm. having been given in three and one-half days.

Alkalis were administered, fluids were forced, and continuous hot compresses were applied to the renal regions. In the next twenty-four hours, despite an intake of 5,000 cc. by mouth and by vein, the patient voided only 200 cc. of urine, which on microscopic examination contained crystals of the drug and blood. The patient was sluggish and drowsy, and there was tenderness at both costovertebral angles. The blood urea nitrogen, which had been 24.2 mg. per hundred cubic centimeters on admission, was 56.7 mg. and the creatine 4.7 mg. At 3:30 p. m. March 28 he was catheterized and 75 cc. of urine was obtained. This contained no albumin but on microscopic examination from 10 to 20 red blood cells per high power field and many crystals of sulfathiazole were found. That evening the patient began to void increasingly large amounts of urine, and improvement was constant thereafter. The blood and crystals disappeared from the urine and the blood urea nitrogen fell to normal.

CASE 2.—L. S., a white man aged 55, entered the Cleveland City Hospital March 7, 1940, ill with type III pneumococcus pneumonia and received sulfathiazole. The initial dose was 4 Gm. followed by 2 Gm. every four hours for twenty-five doses and then 1 Gm. every four hours for twelve doses. The blood levels were 3.0, 4.5, and 1.9 mg. per hundred cubic centimeters on March 8, 11 and 12. The temperature was normal in sixty hours and clinical improvement was obvious.

From March 9 to 13, specimens of urine contained crystals of the drug. On March 13 from 5 to 10 red blood cells per high power field were also present and the patient complained of severe abdominal pain resembling renal colic. The use of the drug was stopped (56 Gm. had been given in five and one-half days). The patient was given 1.3 Gm. (20 grains) of potassium citrate every hour until the urine was alkaline. Fluids were forced.

The next day the patient had a dull aching pain in the left flank. Urinalysis gave about the same results. The following day only an occasional red blood cell could be found in the urine and the patient was better.

### SUMMARY

Thirty-three (61.1 per cent) of fifty-four patients with pneumonia treated with sulfathiazole showed crystals of the drug in the urine, in contrast to sixteen (28.6 per cent) of fifty-six patients treated with sulfapyridine. This is statistically a highly significant difference and probably is explained by the fact that 10.1 Gm. a day of sulfathiazole was required to produce a blood level of 5.8 mg. per hundred cubic centimeters, whereas 5.1 Gm. of sulfapyridine was sufficient to result in a concentration of 5.4 mg. per hundred cubic centimeters.

The incidence of hematuria was 14.8 per cent for the sulfathiazole treated group and 10.7 per cent for sulfapyridine, a difference which is not statistically significant. One patient treated with sulfathiazole had crystals of the drug in the urinary tract which presumably caused hematuria, retention of nitrogenous products and oliguria of about thirty-six hours' duration. Another patient had hematuria and pain resembling renal colic, also presumably caused by crystals of sulfathiazole in the urine.

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## SPONTANEOUS MEDIASTINAL EMPHYSEMA

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In recent years medical men's attention has been called to a syndrome that might aptly be called Hamman's syndrome, since he was the first to describe it.[1] He reported his observations in 1937 and more fully in 1939.[2] His cases had been seen over a period of five years. Scott[3] later in 1937 reported 2 cases with similar signs and sypmptoms. Since that time others have added to this series—Faulkner and Wagner[4] as well as Morey and Sosman.[5] Because of the importance of the subject I wish to add another case to those already published.

Hamman's explanation for the cause of this condition is that, owing to some weakness in an alveolar wall, it ruptures and the released air dissects its way through the fibrous tissue about the blood vessels into the hilus of the lung and thence into the mediastinal tissue. If the amount of escaped air is voluminous enough it is free to dissect further into the cervical tissues. Morey and Sosman[5] suggest that the frequent concomitant partial pneumothorax observed in some of these cases is due to air from a ruptured alveolus dissecting its way to the visceral pleura forming a pleural bleb which later ruptures. The latter assumption seems hardly necessary or justified. Such a pneumothorax might be produced by rupturing or diffusion from a mediastinal emphysematous bleb.

The onset of this condition is usually brought to the patient's attention with the sudden onset of substernal pain or discomfort, which is often referred to the back and shoulders, rarely to the arms. The age incidence in reported cases varies between 16 and 51 years. The duration of the pain varies from five or ten minutes to as many hours. Usually after about two hours or later the patient becomes conscious of a peculiar crackling noise emitting from his chest, coming with each heart beat. Often there is some associated discomfort and usually he discovers that changing positions might free him from this curious noise and discomfort, while lying on the left side usually intensifies or calls to his attention the aforementioned symptoms. Occasionally patients have leukocytosis and fever; rarely cyanosis and dyspnea are evident. There are no pathognomic electrocardiographic changes.

The finding of a peculiar crackling or bubbling sound heard over the precordium, usually best with the patient lying on his left side and occurring with each cardiac systole, first calls attention to the possibility of a mediastinal emphysema. As Hamman[1] states, the demonstration of subcutaneous emphysema in the cervical region or the finding of air in the mediastinum or pneumothorax by roentgen examination makes the diagnosis evident. However, the latter two findings are not always present.

The diagnosis of this condition is important in that other conditions with a more ominous prognosis, such as coronary occlusion, pericarditis, mediastinitis, ruptured aneurysm and

1. Hamman, Louis: Spontaneous Interstitial Emphysema of the Lungs, Tr. A. Am. Physicians **52**: 311, 1937.
2. Hamman, Louis: Spontaneous Mediastinal Emphysema, Bull. Johns Hopkins Hosp. **44**: 1 (Jan.) 1939.
3. Scott, Agnes: Significance of Anginal Syndrome in Acute Spontaneous Pneumomediastinum, Lancet **1**: 1327-1330 (June 5) 1937.
4. Faulkner, W. B., Jr., and Wagner, R. J.: Fatal Spontaneous Pneumothorax and Subcutaneous Emphysema in an Asthmatic, J. Allergy **8**: 267-272 (March) 1937.
5. Morey, J. B., and Sosman, M. C.: Spontaneous Emphysema, Radiology **32**: 19 (Jan.) 1939.

pulmonary embolus, may be forgotten once the diagnosis has been assured. The cases reported have required no treatment except some cases requiring medication for relief of pain.

My case will be reported briefly, as follows:

P. K., a well developed and nourished lawyer, walked into the Bluefield Sanitarium Hospital, Aug. 12, 1940, complaining chiefly of his heart thumping and of the associated clicking with each beat. His past history was noncontributory except possibly for a severe case of whooping cough at 12 years, which, he stated, nearly killed him. He had been feeling perfectly well until August 10, when he awakened about 3 a. m. with paroxysms of coughing that lasted off and on for two hours, interrupting his sleep. This was unusual for him. On awakening again about 8 o'clock he turned on his left side and became conscious of noisy thumping of his heart. He was able to work August 10, although this painful thumping and noise, which even his friends were easily able to hear, persisted. These queer sensations continued on the following day, but by then he was able to gain some relief by deep inspiration or stretching. Becoming very worried about himself, he came to the hospital along with his anxious family, insisting that he had severe heart trouble. A member of our medical staff jokingly reassured him and in turn was amazed when the man turned on his left side and, even while seated at his desk across the room, the physician was able to hear a loud rhythmic crunching noise. On examination the sounds were found to be synchronous with each heart beat.

On examination the patient, who was robust, was in no acute distress but rather apprehensive. He is an intelligent man. The blood pressure was 124 systolic and 74 diastolic, the pulse rate 80 and the temperature 99 F. There was no evidence of subcutaneous emphysema about his neck or shoulders and no evidence of pneumothorax. A percussion note was hyperresonant over the precordial area. The heart sounds were normal with the patient lying flat, but when he turned on the left side a loud clicking, crunching sound could be easily heard over the entire precordium which was almost painful to the ear. This sound was loud on expiration but disappeared entirely on deep inspiration. The noise was constantly present with each cardiac systole under the aforementioned conditions. At times, however, over the apical area a sound which might have been interpreted as a harsh diastolic murmur would come and go during expiration. The patient also demonstrated his ability to produce these former sounds by bending forward while standing. The physical examination was otherwise negative. A roentgen examination revealed the heart and great vessels to be normal, with no evidence of pneumothorax. The leukocyte count was 7,200. The sedimentation rate was 5 mm. in one hour. An electrocardiogram was normal.

Fortunately I had a copy of Dr. Hamman's report, and the diagnosis became obvious. The patient was more relieved after reading this reprint than with any assurance I could give him. After a week's time his complaints and signs had completely disappeared.

I convinced myself about the physical manifestations of mediastinal emphysema by finding about one month later crackling sounds over the precordial area of a patient admitted to the hospital after receiving a stab wound which pierced the mediastinal tissue just to the left of the sternum in the fourth intercostal space. The laceration was sutured, and the following morning crackling, bubbling sounds could be heard synchronous with each heart beat, loudest on forced expiration. The sounds had disappeared by the following afternoon. The patient experienced no discomfort.

### CONCLUSION

1. The most consistent finding in mediastinal emphysema is a crunching, bubbling sound over the precardium synchronous with heart beats.

2. Confirmatory signs are subcutaneous emphysema about the cervical region and the roentgen finding of pneumothorax or evidence of emphysema around the heart or in the mediastinum.

3. Patients usually show few constitutional symptoms.

4. The diagnosis can easily be made if the possibility of mediastinal emphysema is kept in mind.

## *Special Article*

# GLANDULAR PHYSIOLOGY AND THERAPY

## THE NEUROHYPOPHYSIS

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AND
FRANCES K. OLDHAM, PH.D.
CHICAGO

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The neurohypophysis consists of three poorly defined regions: (1) the neural lobe, (2) the infundibular stem and (3) the median eminence (or part thereof[1]). Because of the intimate contact of the neural and the intermediate lobe in man and most laboratory animals, these two parts of the pituitary gland are frequently classed together as the posterior lobe. However, with the clarification of the development and of the secretory capacity of the neural division of the hypophysis, it becomes expedient to abandon the use of a term based purely on gross anatomic relations.

The primary structural elements of the neurohypophysis are pituicytes and unmyelinated nerve fibers. The pituicytes are derived from the ependymal cells of the neural tube and are closely related to neuroglia. They have one or more cytoplasmic processes, and frequently these end in close relation to blood vessels or connective tissue.[2] The nerve fibers have their cells of origin in the supraoptic and tuberal nuclei. They sweep down the infundibular stem in dense bundles and spread out in the neural lobe, forming a rich network about the cells.[3]

### ORIGIN AND PATH OF ESCAPE OF THE SECRETION

It was formerly believed that the so-called "posterior lobe hormones" (pressor, antidiuretic, oxytocic and melanophore-dispersing principles) were elaborated by the pars intermedia. Support for this view came from the close association between the neural and the intermediate lobe in most species and from the reluctance of many investigators to ascribe a secretory role to cells of nervous origin.[4] However, during the past five years, convincing evidence has been adduced to prove that the pressor, antidiuretic and oxytocic hormones arise from the intrinsic elements of the neurohypophysis. In studies of species in which a pars intermedia is lacking (the cetaceans, the armadillo, the chicken

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1. Weaver, T. A., Jr., and Bucy, P. C.: The Anatomical Relationships of the Hypophyseal Stem and the Median Eminence, Endocrinology **27**: 227 (Aug.) 1940.

2. Bucy, P. C.: The Pars Nervosa of the Bovine Hypophysis, J. Comp. Neurol. **50**: 505 (Aug.) 1930. Griffiths, Mervyn: The Relationship Between the Secretory Cells of the Pars Nervosa of the Hypophysis and Classical Neuroglia, Endocrinology **26**: 1032 (June) 1940.

3. Rasmussen, A. T.: Innervation of the Hypophysis, Endocrinology **23**: 263 (Sept.) 1938.

4. Cushing, Harvey: Posterior Pituitary Activity from an Anatomical Standpoint, Am. J. Path. **9**: 539 (Sept.) 1933.

and the South American manatee [5]) it has been shown that these three principles are present in extracts of the neural lobe, whereas the melanophore-dispersing factor is present only in extracts of the anterior lobe.[6] The colloid masses, or Hering bodies, frequently considered to be secretory antecedents migrating from the intermediate lobe into the neurohypophysis, are believed to be fixation artefacts.[7] Interruption of the nerve tracts to the neurohypophysis results in degenerative changes in the pituicytes and loss of pressor, antidiuretic and oxytocic activity.[8] Changes in the pituicytes have been correlated with secretory activity.[9] Tissue cultures of the neural lobe admixed with the intermediate lobe have pressor and melanophore-dispersing activity, while those of the intermediate lobe alone have only melanophore-dispersing activity.[10]

While the evidence points to the pituicytes as the secretory elements, the function of the nerve fibers is not as yet clear. There is evidence that a reflex connection exists between the vagus and the supraoptico-hypophysial tract.[11]

The neurohypophysis receives a fairly rich blood supply from the inferior hypophysial arteries. Its venous drainage is into the circular sinus.[12] Recent failures to detect the posterior lobe principles in cerebrospinal fluid do not support the view once advanced that these principles escape by way of the third ventricle.[13] Massive intravenous doses of pressor and oxytocic substances are excreted in part unchanged in the urine.[14] Efforts to demonstrate these factors in blood or urine under physiologic conditions have yielded contradictory results.[15]

5. Valsö, Jacob: Der Hormongehalt der Hypophyse des Blauwals (Balaenoptera sibbaldii), Klin. Wchnschr. **13:** 1819 (Dec. 22) 1934. Geiling, E. M. K.: The Hypophysis Cerebri of the Finback (Balaenoptera Physalis) and Sperm (Physeter Megalocephalus) Whale, Bull. Johns Hopkins Hosp. **57:** 123 (Sept.) 1935. Geiling, E. M. K., and Oldham, Frances K.: The Site of Formation of the Posterior Lobe Hormones, Tr. A. Am. Physicians **52:** 132, 1937. Oldham, Frances K.: McCleery, D. P., and Geiling, E. M. K.: A Note on the Histology and Pharmacology of the Hypophysis of the Manatee (Trichechus Inunguis), Anat. Rec. **71:** 27 (May 25) 1938. Oldham, Frances K.: The Pharmacology and Anatomy of the Hypophysis of the Armadillo, ibid. **72:** 265 (Nov. 25) 1938.

6. It is generally conceded that in those species possessing a discrete intermediate lobe, the melanophore-dispersing hormone is secreted by the cells thereof.

7. Gersh, Isidore, and Tarr, A. deL.: The So-Called Hyaline Bodies of Herring in the Posterior Lobe of the Hypophysis, Anat. Rec. **63:** 231 (Oct. 25) 1935.

8. Fisher, Charles, and Ingram, W. R.: The Effect of Interruption of the Supraoptico-Hypophyseal Tracts on the Antidiuretic, Pressor and Oxytocic Activity of the Posterior Lobe of the Hypophysis, Endocrinology **20:** 762 (Nov.) 1936.

9. Gersh, Isidore: The Structure and Function of the Aranchymatous Glandular Cells in the Neurohypophysis of the Rat, Am. J. Anat. **64:** 407 (May) 1939. Wang, Kun-jen: A Vagus Post-Pituitary Reflex: V. The Secretory Cells of the Pars Nervosa, Chinese J. Physiol. **13:** 405 (Dec.) 1938.

10. Geiling, E. M. K., and Lewis, M. R.: Further Information Concerning the Melanophore Hormone of the Hypophysis Cerebri, Am. J. Physiol. **113:** 534 (Nov.) 1935. Anderson, Evelyn, and Haymaker, Webb: Elaboration of Hormones by Pituitary Cells Growing in Vitro, Proc. Soc. Exper. Biol. & Med. **33:** 313 (Nov.) 1935.

11. Chang, H. C.: The Establishment of a Vagus-Post-Pituitary Reflex: a Review, Chinese M. J. **56:** 360 (Oct.) 1939. Sattler, D. G.: Vago-Neurohypophyseal Pressor Reflex, Proc. Soc. Exper. Biol. & Med. **44:** 82 (May) 1940.

12. Wislocki, G. B.: The Vascular Supply of the Hypophysis Cerebri of the Rhesus Monkey and Man, Proc. A. Research Nerv. & Ment. Dis., Proc. (1936) **17:** 48, 1938.

13. Van Dyke, H. B.; Bailey, Percival, and Bucy, P. C.: The Oxytocic Substance of the Cerebrospinal Fluid, J. Pharmacol. & Exper. Therap. **36:** 595 (Aug.) 1929. Friedman, Gertrude S., and Friedman, M. H.: An Examination of Cerebrospinal Fluid for Oxytocic Activity as Tested by the Rabbit Uterine Fistula Preparation, Am. J. Physiol. **103:** 244 (Jan.) 1933. Simon, Alexander: The Secretion of the Posterior Lobe of the Hypophysis After the Administration of Drugs, J. Pharmacol. & Exper. Therap. **49:** 375 (Nov.) 1933.

14. Larson, Edward: Tolerance and Fate of the Pressor Principle of Posterior Pituitary Extract in Anesthetized Animals, J. Pharmacol. & Exper. Therap. **62:** 346 (March) 1938; Fate of the Injected Oxytocic Principle of Posterior Pituitary in Anesthetized Dogs, ibid. **67:** 175 (Oct.) 1939.

15. Gilman, Alfred, and Goodman, Louis: The Secretory Response of the Posterior Pituitary to the Need for Water Conservation, J. Physiol. **90:** 113 (July 15) 1937. Walker, A. M.: Experiments upon the Relations Between the Pituitary Gland and Water Diuresis, Am. J. Physiol. **127:** 541 (Oct.) 1939.

## CHEMISTRY OF EXTRACTS OF THE POSTERIOR LOBE

Although several commercial preparations of the posterior lobe of the hypophysis are available for clinical use, as yet none of the active principles have been isolated as chemically pure entities. Abel and his associates [16] have isolated a tartrate of high purity possessing pressor, oxytocic and antidiuretic properties. Kamm and co-workers [17] and more recently Stehle [18] and others have separated from pituitary extracts two fractions, pitressin and pitocin, which have been highly purified.

The treatment of posterior pituitary preparations with enzymes has given rise to results which are subject to different interpretations.[19] Gulland and his associates reported that an inactivating enzyme accompanies preparations of dipeptidase, aminopolypeptidase, trypsin and papain but that it is not identical with any of these. Larson confirmed the reports of earlier workers and expressed the opinion that the inactivation is due to the aminopeptidases of the tissue ereptases. He suggested that this enzymatic process may be one of the factors in the diminution of pressor response to successive doses of pituitary extract. Thus far, no enzyme acting in an acid range has been found that will destroy the active factors of the posterior lobe. Indubitably, other factors, besides enzymes, cause loss of activity, such as adsorption, hydrogen ion concentration, incubation time and temperature.[20]

Recent studies on electrophoresis indicate that both the pressor and the oxytocic principle are possibly amphoteric and are certainly basic in nature.[21] When such experiments are conducted in a medium below a certain $p_H$ (the value of which differs in each report) the oxytocic substance migrates to the cathode. According to duVigneaud and his associates, the pressor substance migrates in the same direction at an even more rapid rate, since its concentration in the cathode vessel is greater than that of the oxytocic substance. Irving and duVigneaud repeated this experiment on the press juice from fresh glands with the same general result. This they advanced as evidence that the two principles exist as separate entities in the natural state.[22]

16. Abel, J. J.; Rouiller, C. A., and Geiling, E. M. K.: Further Investigations on the Oxytocic-Pressor-Diuretic Principle of the Infundibular Portion of the Pituitary Gland, J. Pharmacol. & Exper. Therap. **22:** 289 (Nov.) 1923.

17. Kamm, Oliver; Aldrich, T. B.; Grote, I. W.; Rowe, L. W., and Bugbee, E. P.: The Active Principles of the Posterior Lobe of the Pituitary Gland: I. The Demonstration of the Presence of Two Active Principles; II. The Separation of the Two Principles and Their Concentration in the Form of Potent Solid Preparations, J. Am. Chem. Soc. **50:** 573 (Feb.) 1928.

18. Stehle, R. L.: New Method for Separating Pressor and Oxytocic Substances from Posterior Lobe of Pituitary Gland, J. Biol. Chem. **102:** 573 (Oct.) 1933.

19. (*a*) Gulland, J. M., and MacRae, T. F.: The Oxytocic Hormone of the Posterior Pituitary: III. The Action of Plant Proteolytic Enzymes, Biochem. J. **27:** 1237, 1933; IV. The Action of Animal Proteolytic Enzymes, ibid. **27:** 1383, 1933. (*b*) Dale, H. H., and Dudley, H. W.: On the Pituitary Active Principles and Histamine, J. Pharmacol. & Exper. Therap. **18:** 27 (Aug.) 1921. (*c*) Thorpe, W. V.: Experiments on the Chemical Nature of the Oxytocic Principle in the Pituitary Gland, Biochem. J. **20:** 374, 1926. (*d*) Freudenberg, Karl; Weiss, Emil, and Biller, Hans: Notiz über Oxytocin, Ztschr. f. physiol. Chem. **233:** 172, 1935. (*e*) Heller, H., and Urban, F. F.: The Fate of the Antidiuretic Principle of Post Pituitary Extracts in Vivo and in Vitro, J. Physiol. **85:** 502, 1935. (*f*) Heller, H.: The State in the Blood and the Excretion in the Kidney of the Antidiuretic Principle of the Posterior Pituitary Extracts, ibid. **89:** 81 (Feb. 19) 1937.

20. Vaichulis, J. A.: The Effect on the Posterior Pituitary Principles of Incubating Beef Heads at Thirty-Seven Degrees Centigrade for Twenty-Four Hours, J. Pharmacol. & Exper. Therap. **63:** 37 (May) 1938, A Simple Method of Removing the Oxytocic Principle from the Posterior Lobe of the Beef Pituitary Glands, ibid. **66:** 37 (May) 1939.

21. Das, N.; Ghosh, B. N., and Guha, B. C.: Bemerkung zur Elektrodialyse von Oxytocin, Ztschr. f. physiol. Chem. **238:** 131, 1936. Gulland, J. M.; Lucas, N. S.; Freeman, M., and Randall, S. S.: The Oxytocic Hormone—Ultra Violet Absorption Spectra, Adsorption, and Electrodialysis, Biochem. J. **29:** 2208, 1935. du Vigneaud, Vincent; Irving, G. W., Jr.; Dyer, H. M., and Sealock, R. R.: Electrophoresis of Posterior Pituitary Preparation, J. Biol. Chem. **123:** 45 (March) 1938.

22. Irving, G. W., Jr., and du Vigneaud, Vincent: The Differential Migration of the Pressor and Oxytocic Hormones in Electrophoretic Studies of the Untreated Press Juice of the Posterior Lobe of the Pituitary Gland, J. Biol. Chem. **123:** 485 (April) 1938.

A preliminary study by Rosenfeld of sedimentation properties in the ultracentrifuge indicates that the pressor and oxytocic principles exist normally as relatively large molecules, which are broken down to smaller, physiologically active products by the usual methods of chemical extraction.[23]

Perhaps the most significant recent chemical finding has been the demonstration in three separate laboratories that the pressor and the oxytocic factor each possesses at least one reduction-oxidation system, presumably connected with the S-S group of cysteine.[24]

Analytic work by Stehle and others on highly purified preparations indicates a high amino acid content in both pressor and oxytocic principles. The amino acids found in largest amounts are cysteine, tyrosine and arginine.[25]

Many of the problems relating to the chemical and the physiologic actions of these substances must await final solution until the "mother substance" of Abel,[26] or the fractions derived therefrom or existing separately, are obtained as chemically pure compounds. These should be of astounding potency, judging from the high degree of physiologic activity exhibited by impure preparations.

At present there is available an international pituitary powder, against which all commercial preparations are standardized. The unit of pituitary potency is the activity contained in 0.5 mg. of the standard pituitary powder (U. S. P. XI).

### PHYSIOLOGIC EFFECTS

Posterior pituitary extract (solution of posterior pituitary U. S. P. XI) exerts striking physiologic actions on the cardiovascular, respiratory and renal systems, on smooth muscle, on certain glandular structures and on the metabolism. The separation of pitressin and of pitocin from pituitary extracts necessitated apportioning these multiple pharmacodynamic actions. Pitressin elicits the cardiovascular, respiratory, renal, intestinal and certain metabolic effects, and pitocin the oxytocic action. Both substances cause hyperglycemia and act as antagonists to insulin. The mechanism of action of each in this respect is probably different, and the relative effectiveness depends on the species of animal used.[27]

### CARDIOVASCULAR AND METABOLIC EFFECTS

In man, therapeutic doses of either solution of pituitary U. S. P. or of pitressin, given intramuscularly or subcutaneously, do not cause any significant rise of blood pressure, in spite of the marked pallor, which would lead one to infer that the arterial tension is elevated.[28] There is a decided but brief fall in the pulse rate, oxygen consumption and cardiac output, which is followed by a more prolonged rise.[29] Pitocin causes only a slight increase in oxygen consumption and negligible changes in the circulation. The decreased cardiac output after the injection of solution of pituitary or of pitressin is due largely to coronary constriction, which may be obviated by the administration of epinephrine or ephedrine.[30] The subsequent elevation in cardiac output and pulse rate is due to the accumulation of catabolites during the period of decreased consumption of oxygen after the administration of these drugs. This accumulation of catabolites causes a condition of "oxygen debt," the liquidation of which is manifested in the later increase in oxygen consumption.

In trained unanesthetized dogs the effects of these drugs in larger doses per kilogram of body weight, given intravenously, are more intense but essentially similar to those found in man, except for the blood pressure.[31]

In experimental animals the blood pressure response to solution of pituitary and to pitressin is determined by several factors, such as dose, time between injections, type and depth of anesthesia and species of experimental subject. Small doses given to normal anesthetized dogs or cats cause peripheral vasoconstriction with a sharp rise of pressure. Repeated doses give a lessened response, and tolerance is easily acquired. Larger doses given to intact animals with or without anesthesia may cause a fall in pressure followed by a rise. The depressor effect is due to coronary constriction.[30] In experiments in which cardiac effects are eliminated by the use of the Gibbs artificial heart, large doses of solution of posterior pituitary or of pitressin invariably cause a sharp rise of pressure, and subsequent injections produce little or no effect. Such experiments indicate that the depressor action is cardiac and that the tolerance factor is vested in the peripheral structures. In the fowl, pitocin gives a fall in pressure. This is a quantitative reaction and has been adapted as a method of assay for the oxytocic principle.[32]

### RESPIRATORY EFFECTS

The respiratory changes are secondary to the circulatory effects. In unanesthetized animals there is a quickening of the respiratory rate interspersed with periods of cessation of breathing.[16]

### RENAL EFFECTS: DIURETIC-ANTIDIURETIC ACTION

While the antidiuretic action of posterior pituitary is generally associated with the pressor fraction, recent studies by Heller suggest that it may be due to a separate entity, since heat inactivation of the pressor principle proceeds at a faster rate than that of the anti-

23. Rosenfeld, Morris: The Native Hormones of the Posterior Pituitary Gland: The Pressor and Oxytocic Principles, Bull. Johns Hopkins Hosp. **66:** 398 (June) 1940.

24. Gulland, J. M., and Newton, S. S.: The Oxytocic Hormone of the Posterior Lobe of the Pituitary Gland: V. Recognition as an Oxidation-Reduction System, Biochem. J. **29:** 378, 1935. Sealock, R. R., and du Vigneaud, Vincent: Studies on the Reduction of Pitressin and Pitocin with Cysteine, J. Pharmacol. & Exper. Therap. **54:** 433 (Aug.) 1935. Freudenberg and others.[19d]

25. du Vigneaud, Vincent; Sealock, R. R.; Sifferd, R. H.; Kamm, Oliver, and Grote, I. W.: Some Chemical Properties of Highly Purified Preparations of Pitressin and Pitocin, J. Biol. Chem. **100:** xciv (May) 1933. Stehle, R. L., and Fraser, A. M.: The Purification of the Pressor and Oxytocic Hormones of the Pituitary Gland and Some Observations on the Chemistry of the Products, J. Pharmacol. & Exper. Therap. **55:** 136 (Oct.) 1935. Stehle, R. L., and Trister, S. M.: Additional Data Concerning the Chemistry of the Pressor and Oxytocic Hormones of the Pituitary Gland, ibid. **65:** 343 (April) 1939.

26. Abel, J. J.: On the Unitary versus the Multiple Hormone Theory of Posterior Pituitary Principles, J. Pharmacol. & Exper. Therap. **40:** 139 (Oct.) 1930.

27. Ellsworth, H. C.: The Antagonism Between Posterior Lobe Pituitary Hormones and Insulin, J. Pharmacol. & Exper. Therap. **56:** 417 (April) 1936. Holman, D. V., and Ellsworth, H. C.: The Hyperglycemic Constituent of Posterior Pituitary Extract, ibid. **53:** 377 (March) 1935. Ellsworth, H. C.: The Action of Posterior Pituitary Hormone upon the Blood Sugar of the Rabbit, ibid. **55:** 435 (Dec.) 1935.

28. Moffat, W. M.: The Effect of Pituitrin Injections on Blood Pressure in Man, Am. J. M. Sc. **186:** 854 (Dec.) 1933.

29. Grollman, Arthur, and Geiling, E. M. K.: The Cardiovascular and Metabolic Reactions of Man to the Intramuscular Injection of Posterior Pituitary Liquid (Pituitrin), Pitressin, and Pitocin, J. Pharmacol. & Exper. Therap. **46:** 447 (Dec.) 1932.

30. Melville, K. I., and Stehle, R. L.: The Antagonistic Action of Ephedrine (or Adrenalin) upon the Coronary Constriction Produced by Pituitary Extract and Its Effect upon Blood Pressure, J. Pharmacol. & Exper. Therap. **42:** 455 (Aug.) 1931. Melville, K. I.: The Electrographic and Blood Pressure Changes Induced by Posterior Pituitary Extract (Postlobin-V) and the Influence of Ephedrine Thereon, ibid. **64:** 86 (Sept.) 1938; The Action of Pituitary Extract on the Blood Pressure of the Normal Unanesthetised Animal and the Effect of Ephedrine or Adrenaline Thereon, ibid. **47:** 355 (March) 1933. Ross, J. B.; Dreyer, N. B., and Stehle, R. L.: The Cardiac Action of Pituitary Extract (Posterior Lobe), ibid. **38:** 461 (April) 1930.

31. Geiling, E. M. K., and DeLawder, A. M.: Metabolic Changes Following the Intravenous Injection of Posterior Pituitary Extracts and Their Correlation with the Well Known Pharmacodynamic Action of the Drugs, Bull. John Hopkins Hosp. **51:** 1 (July) 1932.

32. Coon, J. M.: A New Method for the Assay of Posterior Pituitary Extracts, Arch. internat. de pharmacodyn. et de thérap. **62:** 79 (May 31) 1939.

diuretic principle.[33] Therapeutic doses of either solution of pituitary or pitressin cause a marked antidiuretic effect lasting some hours in patients with diabetes insipidus or in normal subjects who have previously ingested water by mouth. This action is apparently a renal effect due to increased reabsorption of water by certain cells of the tubule.[34] Extrarenal effects, such as changes in the blood electrolytes [35] or inhibition of some hypothetic water center in the hypothalamus,[36] are probably of only secondary importance in the diuresis-inhibiting action of posterior pituitary.

A diuretic effect is best elicited with anesthetized rabbits rendered diuretic by feeding of greens, by rapid intravenous infusion of isotonic sucrose or by administration of phlorhizin. Unanesthetized animals with low urine flow may also respond in this way. This diuresis may be due to increased glomerular filtration or to decreased reabsorption of water by the tubules. According to Heller, the diuretic effect is due to the pressor and not to the antidiuretic principle.[37]

### ACTION ON THE GASTROINTESTINAL TRACT

Variations in species of animal, in technic and in the portion of the gastrointestinal tract used account for the lack of concordance in the results obtained by different workers with preparations of the posterior pituitary principles. In the unanesthetized dog pitressin stimulates intestinal activity and causes defecation, while the oxytocic substance has an antagonistic influence in respect to these actions.[38]

Massive doses of posterior pituitary preparations give rise to gastric ulcers, due probably to local ischemic action by the pressor principle.[39]

### OXYTOCIC EFFECTS

A number of workers [40] by in vitro and in vivo experiments on the uterus have made it clear that the nature and the degree of the reaction of the uterine musculature to posterior lobe preparations depend on (*a*) the species of the animal, (*b*) the phase of the menstrual or estrous cycle, (*c*) whether the uterus is gravid or nongravid and (*d*) the stage of pregnancy —early or late, in parturition or in the puerperium. Some of the variations in the uterine response become more intelligible when viewed in the light of the newer researches dealing with the effect on the uterus of the estrogenic and corpus luteum hormones and their interplay with the hormones from the anterior and posterior lobes of the pituitary. Briefly stated, the reaction of the uterine muscle to pituitary preparations is markedly affected by the nature of that ovarian, placental or anterior pituitary hormone whose influence is preponderant at the time of injection. During the early stages of pregnancy the human uterus does not react to pitocin, probably because of the inhibitory effect of the luteal secretion. It does, however, respond to small doses of pitressin; whether the response is due to an effect of the drug per se or to mechanical factors remains a moot point. Later in the gestation period the reactivity to pitocin returns, and during parturition the uterus is very reactive to this substance and also to solution of pituitary. It is at this time that these drugs are mainly used by obstetricians. The influence of estrogenic substances in rendering the uterus more highly reactive comes into play here. In the puerperium, however, while involution is in progress, pitocin evokes little or no response.

In respect to the nongravid human uterus, both in vitro and in vivo studies indicate that pitressin is more effective than pitocin in eliciting contractions. According to Knaus, the uterus is highly reactive to posterior pituitary preparations during the first half of the menstrual cycle, but during the second half the reactivity is low. He attributed these changes to the liberation of progesterone following ovulation, and he presented these findings as evidence in support of the Ogino-Knaus theory of periodic fertility in women. Certain other investigators have been unable to confirm Knaus's findings.

For a more detailed discussion of the problem, the recent work of Reynolds should be consulted.[41]

The excised horns of the virgin guinea pig's uterus are very reactive to solution of pituitary and to pitocin; this action forms the basis of the official method of assay of these drugs.

### CLINICAL USES

Solution of posterior pituitary was introduced into obstetrics by Blair Bell and Hofbauer.[42] Its use is now largely restricted to the control of postpartum bleeding in the third stage of labor and to the prevention or control of hemorrhage in therapeutic abortions. In some clinics, both here and abroad, intranasal application or cautious use of small intramuscular doses following administration of castor oil and quinine is advocated for induction of labor. However, rupture of the uterus, fetal asphyxia or even death, laceration of the cervix with hemorrhage or infection, secondary atony of the uterus with thrombosis and embolism, and cardiac death from sudden overexertion have all occurred from the misuse of pituitary preparations during labor.[43] Its use during the second stage of labor, to hasten separation of the placenta and to decrease bleeding during the third stage, may lead to hourglass contraction of the uterus necessitating manual removal

33. Heller, H.: The Effect of the Hydrogen Ion Concentration on the Stability of the Anti-Diuretic and Vasopressor Activities of Posterior Pituitary Extracts, J. Physiol. **96:** 337 (Aug. 14) 1939.

34. Burgess, W. W.; Harvey, A. M., and Marshall, E. K., Jr.: The Site of the Anti-Diuretic Action of Pituitary Extract, J. Pharmacol. & Exper. Therap. **49:** 237 (Oct.) 1933. Gersh, Isidore: Reabsorption of Water During Pituitary Anti-Diuresis, ibid. **52:** 231 (Oct.) 1934.

35. Stehle, R. L., and Bourne, W.: The Effect of Pituitary Extract on the Secretion and Composition of the Urine, J. Physiol. **60:** 229 (July) 1925.

36. Molitor, H., and Pick, E. P.: Ueber die Bedeutung des Gewebswassers fur die Wirkung diuresebeeinflussender Arzneimittel: I. Der Einfluss von Flüssigkeitsanreicherung auf die Stärke der Pituitrinwirkung, Arch. internat. de pharmacodyn. et de thérap. **38:** 279, 1930.

37. Heller, H.: The Action of the Anti-Diuretic Principle of Posterior Pituitary on the Urine Excretion of Anesthetized Animals, J. Physiol. **98:** 405 (Aug.) 1940.

38. Melville, K. I.: Pressor and Oxytocic Fractions of Posterior Pituitary Extract; Comparative Effects on Blood Pressure and Intestinal Activity, J. A. M. A. **106:** 102 (Jan. 11) 1936.

39. Dodds, E. C.; Noble, R. L., and Smith, E. R.: A Gastric Lesion Produced by an Extract of the Pituitary Gland, Lancet **2:** 918 (Oct. 27) 1934.

40. Knaus, Hermann: Die periodische Fruchtbarkeit und Unfruchtbarkeit des Weibes, Vienna, E. Maudrich, 1934. Robson, J. M.: Recent Advances in Sex and Reproductive Physiology, Philadelphia, P. Blakiston's Son & Co., 1934. Reynolds, S. R. M.: The Effect of Certain Calcium Salts on the Rhythmically Contracting and Quiescent Uterine Fistula, with Observations on the Action of Posterior Pituitary Extracts, Am. J. Physiol. **105:** 358 (Aug.) 1933. Moir, Chassar: Recording the Contraction of the Human Pregnant and Nonpregnant Uterus, Tr. Edinburgh Obst. Soc., 1933-1934, p. 93, in Edinburgh M. J., August 1934. Adair, F. L., and Haugen, J. A.: A Study of Suspended Uterine Muscle Strips in Vitro, Am. J. Obst. & Gynec. **37:** 753 (May) 1939. McLellan, Archibald: Response of Non-Gravid Human Uterus to Posterior Pituitary Extract, Lancet **1:** 919 (May 18) 1940.

41. Reynolds, S. R. M.: Physiology of the Uterus, New York, Paul B. Hoeber, Inc., 1939.

42. Bell, W. B.: The Pituitary Body and the Therapeutic Value of the Infundibular Extract in Shock, Uterine Atony, and Intestinal Paresis, Brit. M. J. **2:** 1609, 1909. Hofbauer, J.: Hypophysenextrakt als Wehenmittel, Zentralbl. f. Gynäk. **35:** 137, 1911.

43. Davis, M. E.: The Use and Abuse of Ergot and Pituitary, J. A. M. A. **109:** 1631 (Nov. 13) 1937. Sharkey, J. A.: Should Solution of Posterior Pituitary Be Used in the First and Second Stages of Labor? ibid. **115:** 1315 (Oct. 19) 1940. Pendleton, G. F.: Abuse of Solution of Posterior Pituitary During Early Labor, ibid. **115:** 1318 (Oct. 19) 1940. DeLee, J. B.: The Use of Solution of Posterior Pituitary in Modern Obstetrics, ibid. **115:** 1320 (Oct. 19) 1940.

and hence increasing the dangers of puerperal fever. The use of posterior pituitary extract during the puerperium to hasten involution is the practice of some obstetricians in the belief that poor involution increases the chances of pelvic infection. Others believe that it is bad practice to aggravate a uterus that tends to wall off infection by reduced activity.

In the normal parturient patient, posterior pituitary in therapeutic doses usually produces no effect on the blood pressure. In the patient with eclampsia or preeclampsia, however, there are marked rise in blood pressure and decrease in urine volume.[44] Dieckmann and Michel have suggested "the pituitrin cold pressor test" (repeated cautious injections of pitressin) as an aid in detecting potential toxemia and in differentiating preeclampsia from the other forms of toxemia.

Posterior pituitary or its pressor fraction is of greatest value in the treatment of diabetes insipidus. This condition is characterized by persistent polyuria, the urine being of low specific gravity, and polydipsia, which is secondary to the polyuria.[45] Both clinical and experimental studies support the view that diabetes insipidus is due to changes in the neurohypophysis resulting in loss of or diminution in the antidiuretic substance.[46] That the anterior lobe plays an important role in water metabolism is attested by the fact that complete hypophysectomy results in transient diabetes insipidus only. It has been suggested that the anterior lobe gives rise to a diuretic substance which normally antagonizes the antidiuretic action of the neurohypophysis. It is thought that this diuretic substance may act through the thyroid gland, probably through the intermediation of the thyrotropic principle of the anterior lobe.[47]

Other clinical uses for the pressor fraction are found in the treatment of paralytic ileus, in the allaying of postoperative distention[48] and in cholecystography, to reduce intestinal flatus.[49] The combination of pitressin with ephedrine has been advocated for the maintenance of blood pressure during spinal anesthesia.[50] The ephedrine, in addition to giving a transient rise in blood pressure, antagonizes the coronary constrictor action of the pitressin.[30] For the alleviation of the polyuria and polydipsia of diabetes insipidus, nasal insufflation of the dry powder has been used with success, while both clinical and experimental attempts have been made to prolong the action of subcutaneous or intramuscular injections by administering the pituitary preparation with zinc salts or in oil.[51] Further work is required for a proper evaluation of these newer preparations.

### DISEASES ASCRIBED TO HYPERSECRETION

In recent years, attempts have been made to associate preeclampsia and eclampsia with hypersecretion of the posterior lobe of the pituitary. However, attempts to demonstrate the presence of the active principles in the blood or urine of patients with these conditions have yielded variable results.[52] The possibility remains that the body becomes unusually sensitive to pituitary substances and support for this view comes from the work of Dieckmann and Michel, Lambillon and others.[44] Further study will be required to establish the role of the neurohypophysis in hypertension.[53]

### HYPERSENSITIVITY TO POSTERIOR PITUITARY

Several cases of hypersensitivity to posterior pituitary have been reported.[54] The symptoms are those of shock: marked pallor, rapid pulse, fall in blood pressure, air hunger, sense of impending death and, in more severe cases, edema and semiconsciousness. These symptoms are alleviated by epinephrine.

### CONCLUSION

While, perhaps, one still cannot assign with certainty any specific roles to the powerful principles of the posterior lobe, nevertheless, in recent years much evidence, both clinical and experimental, has accumulated which indicates that the pressor substance plays an important role in water metabolism.[55] In regard to the oxytocic fraction, opinion is still divided as to whether or not it is a factor in the initiation of uterine contractions during labor. Of interest in this respect is the report by Fisher and co-workers that in cats suffering from experimental diabetes insipidus there developed striking disturbances in the mechanism of parturition.[56] The wide use of solution of posterior pituitary and of preparations of various fractions from the posterior lobe in both surgery and obstetrics justifies the furtherance of experimental studies to establish the chemical composition of the active principles, to determine their mechanism of action and to discover their role in the normal economy of the body.

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# The Chemical Laboratory

THE A. M. A. CHEMICAL LABORATORY HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT. PAUL NICHOLAS LEECH, Director.[1]

## CRYSTALLINE SULFATHIAZOLE

Chemical and pharmacologic data on the compound 2-(*p*-aminobenzenesulfonamido)-thiazole, for which the nonproprietary name sulfathiazole has been adopted by the Council on Pharmacy and Chemistry, were published by Fosbinder and Walter[2] in August 1939. Intense interest in sulfanilamide and its derivatives on the part of the medical profession prompted commercial production of sulfathiazole in quantities sufficient for thorough clinical evaluation. In June 1940, specimens of commercial sulfathiazole were presented to the A. M. A. Chemical Laboratory for examination at the request of the Council on Pharmacy and Chemistry. Preliminary investigation of the submitted brands of sulfathiazole by Dr. E. W. Schoeffel, a former member of the Laboratory staff, led to the discovery of a peculiarity in the melting characteristics of this compound. This information was transmitted to Dr. Theodore G. Klumpp, Chief, Drug Division, U. S. Food and Drug Administration, who instigated an investigation mentioned later. The melting points were determined by two methods: (*a*) the method given in the U. S. P. XI and (*b*) a method which involves observation of small quantities of material on an electrically heated stage under a microscope. Each method is susceptible of standardization against National Bureau of Standards calibrated thermometers.

The first of two specimens of sulfathiazole supplied by the Maltbie Chemical Company was found to melt at about 178 C.; the second was found to contain some crystals which melted at about 178 C., together with a bulk of material which melted at about 202 C. This information was in contrast to melting point data found for portions of specimens of sulfathiazole submitted by the Calco Chemical Division American Cyanamid Company,

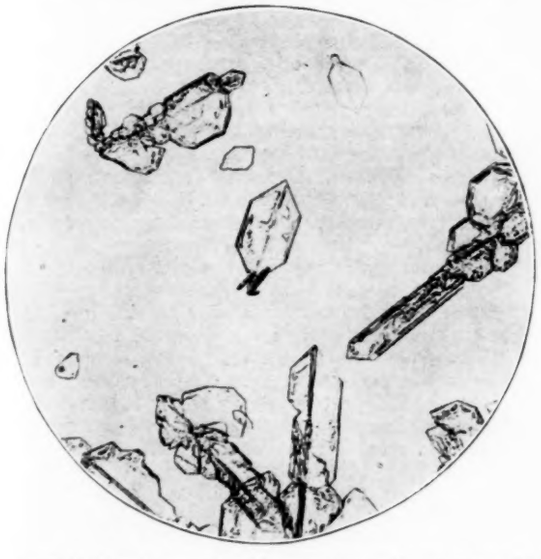

Fig. 1.—Sulfathiazole crystals with a melting point of about 175 C.

Merck & Co., Inc., and the Lederle Laboratories, Inc. It was found that each of these specimens melted at from 202 to 203 C., when heated according to the U. S. P. XI method. Close observation revealed a transient but characteristic phenomenon between 172 and 178 C. In each instance the column of solid within the heated capillary slumped very slightly and minute molten globules appeared; the latter seemed to wet the glass and resolidify almost immediately. Under the microscope, all these specimens were found to exhibit varying amounts of material which melted at 172-178 C., some material which underwent a structural transformation in the solid state and finally melted at 200-203 C., and a preponderant amount of material which melted at 201-203 C.

Portions of each of the submitted specimens of sulfathiazole were recrystallized from boiling 95 per cent ethyl alcohol. Long, acicular crystals and massive, hexagonal, platelike crystals were obtained. The two crystalline forms were dried and examined under the microscope on the electrically heated stage. The needle-like crystals were found to melt at 202-203 C. The

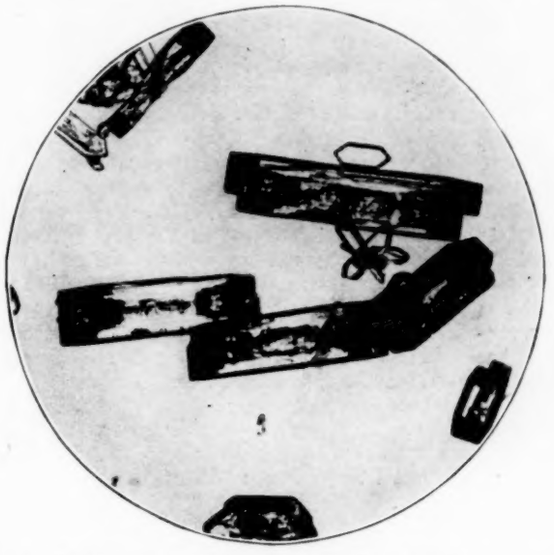

Fig. 2.—Sulfathiazole crystals (pseudomorphic habit) with a melting point of about 202 C.

platelike crystals were found to behave variously as follows: (1) Some of the crystals melted at 172-175 C. and remained molten; (2) some of the crystals melted at 172-175 C., followed by resolidification of the molten mass, which finally remelted at 200-203 C.; (3) some of the crystals exhibited a structural transformation in the solid state at 172-175 C. and finally melted at 201-203 C. From the latter observation it was apparent that an alteration in the structure of the crystals, induced by heat, resulted in a higher melting point. Accordingly, the original specimen of sulfathiazole which had been found to melt completely at about 175-178 C. was placed in an oven at 105 C. for five hours. The melting point of the specimen was then found to be from 202 to 203 C., with only a few crystals which showed transition in the solid state at 172-178 C.

The foregoing data on sulfathiazole indicated that this compound exhibits dimorphism, or the ability to exist in the solid state in two crystalline configurations. The observations have been confirmed by Grove and Keenan[3] in the chemical laboratories of the U. S. Food and Drug Administration, who have reported additional chemical data and optical properties of the two crystalline forms.

Since sulfathiazole is soluble in both acids and bases, it was decided to examine crystals of sulfathiazole precipitated from acid solution by the addition of sufficient base and crystals of sulfathiazole precipitated from basic solution by the addition of sufficient acid. It was thought that two crystalline modifications might be obtained. It was found, however, that the crystalline habit of sulfathiazole in the form which melts at 172-175 C. varies with the method of precipitation. Crystals of sulfathiazole obtained by neutralization of a clear hydrochloric acid solution of sulfathiazole appear as thin hexagonal plates (fig. 1). These crystals melt unchanged at 172-175 C. and apparently resist transformation in the solid state on prolonged heating at 100-105 C. Crystals of sulfathiazole obtained by neutralization of a clear sodium hydroxide solution of sulfathiazole appear in the form of thick, elongated hexagonal plates (fig. 2). When heated rapidly, these crystals melt at 172-175 C. However, they readily undergo a transition in the solid state at this temperature, and

1. This was the last report prepared under Dr. Leech's direction before his death suddenly on January 14.

2. Fosbinder, R. J., and Walter, L. A.: Sulfanilamide Derivatives of Heterocyclic Amines, J. Am. Chem. Soc. **61**: 2032 (Aug.) 1939.

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the resulting pseudomorphic habit melts at 201-203 C. This same transformation may be produced by prolonged heating of the thick, elongated plates at a temperature of 100-105 C. without change in the gross appearance of the crystal form.

The method used in the preparation of the two differently melting types of sulfathiazole is as follows:

(*a*) Place 25 Gm. of sulfathiazole and 250 cc. of distilled water in a 500 cc. beaker. Stir the mixture mechanically, and slowly add 20 cc. of concentrated hydrochloric acid. Continue to stir the mixture for several minutes and filter the resulting solution. Slowly neutralize the constantly stirred filtrate with 2 normal sodium hydroxide. Collect the glistening white precipitate on a Buchner funnel and wash the crystals with distilled water until chlorides are absent from the washings. Spread the thoroughly drained product on a large watch glass and dry it in an oven maintained at 100-105 C. for from two to three hours. The melting point of the product is from 172 to 175 C.

(*b*) Place 25 Gm. of sulfathiazole and 250 cc. of distilled water in a 500 cc. beaker, stir mechanically, and slowly add 4 Gm. of sodium hydroxide dissolved in 25 cc. of water. Filter the resulting solution and neutralize the filtrate with normal hydrochloric acid. Collect, wash and dry the heavy precipitate as described but continue to heat for twelve hours at 100-105 C. The melting point of the product is from 201 to 203 C.

That a difference in pharmacologic activity exists between the two crystalline modifications as striking as the melting point difference is questionable. Accordingly, the toxicity of quantities of each of the two differently melting types of sulfathiazole, prepared as described, is being investigated by Dr. Raymond N. Bieter of the Department of Pharmacology of the University of Minnesota Medical School, who will report his results in a separate publication.

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# Council on Pharmacy and Chemistry

## NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

PAUL NICHOLAS LEECH, Secretary.

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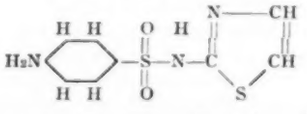
**SULFATHIAZOLE.**—2-sulfanilamidothiazole.—2-sulfanilylaminothiazole.—2(*p*-aminobenzenesulfonamido) thiazole.—4-aminobenzenesulfonyl-2-aminothiazole.—$C_9H_9O_2N_3S_2$.—Sulfathiazole has the following structural formula:



It may be prepared by the condensation of *p*-acetylaminobenzenesulfonylchloride with 2-aminothiazole in pyridine. The compound 2(*p*-acetylamino-benzenesulfonamido) thiazole separates on dilution of the reaction mixture with water and is subsequently hydrolyzed with hydrochloric acid. Sulfathiazole is then isolated by neutralization of the acid solution to congo red and purified by recrystallization from alcohol.

*Actions and Uses.*—Sulfathiazole has been reported to show definite chemotherapeutic effects in experimental infections in mice produced by the inoculation of pneumococci, meningococci, beta hemolytic streptococci, staphylococci, Escherichia coli or the virus of lymphogranuloma venereum. Comparative tests have shown that sulfathiazole is equal to sulfapyridine in its chemotherapeutic effects in experimental pneumococcic infections in mice and that it is somewhat superior to sulfanilamide or sulfapyridine in the control of experimental infections in mice produced by Staphylococcus aureus or E. coli.

Its mode of action is probably similar to that of sulfanilamide, namely to render the blood, spinal fluid, urine and other tissue fluids unfavorable as a medium for supporting the active multiplication of susceptible bacteria. In consequence, tissue invasion by these organisms may be prevented, the production of toxic substances reduced and the antibacterial immune mechanisms of the host permitted to complete the recovery from infection.

Sulfathiazole has been used primarily in the treatment of infections due to the pneumococcus, i. e. pneumococcic pneumonia, and of severe infections due to Staphylococcus aureus. There is evidence to show that the drug is chemotherapeutically effective in the control of tissue infections produced by E. coli; and it is known on the basis of clinical tests that the drug is an effective chemotherapeutic agent in the treatment of gonorrhea in the male. Its use in urinary tract infections produced by E. coli, Streptococcus faecalis, Staphylococcus aureus or Bacillus pyocyaneus is still in the experimental stage.

Sulfathiazole resembles sulfanilamide in certain of its pharmacologic effects. In most patients it is rapidly absorbed when administered by mouth, maximum concentrations of the drug in the blood being obtained in three to six hours after the administration of a single dose. It is fairly evenly distributed throughout most of the body tissues with the exception that it does not pass readily into the spinal fluid. In the tissues a certain proportion of the drug is conjugated to the therapeutically inactive acetyl derivative. The degree of conjugation is, as a rule, slightly greater than that noted for sulfanilamide, but generally less than that for sulfapyridine. It is excreted rapidly by the kidneys and because of this it is sometimes difficult to maintain adequate concentration of the drug in the blood and tissues. If kidney function is impaired the excretion of sulfathiazole will be reduced and the drug will accumulate in the blood and tissues.

In the urine considerably less sulfathiazole is found in the conjugated form than has been generally noted for either sulfanilamide or sulfapyridine. The excretion of the drug is generally almost complete within twenty-four hours after the administration of a single dose of the compound.

*Toxicity.*—The toxic manifestations noted in the course of sulfathiazole therapy are similar to those previously noted in the course of therapy with sulfanilamide or sulfapyridine. These untoward effects are unpredictable in their occurrence and are considered to be the result of an idiosyncrasy to the drug.

Patients who are receiving this drug should be seen daily by their physician in order that any possible toxic effects arising in the course of the administration of sulfathiazole may be noted and appropriate steps taken to eliminate the drug.

Sulfathiazole causes less nausea, vomiting and dizziness than does sulfapyridine; mental disturbances or psychoses are uncommon. Questionable so-called peripheral neuritis has been reported. Cyanosis is generally mild if present, and acidosis has not been noted. Drug fever is very common in the course of treatment with sulfathiazole, having been observed in about 10 per cent of the patients who are receiving this drug. It generally occurs between the fifth and ninth days of treatment but may occur at any period. Drug rashes with or without fever are more frequent in the course of sulfathiazole therapy than when sulfapyridine is being prescribed. The drug may produce all types of rashes. Urticarial or nodular rashes resembling erythema nodosum are often seen.

Hepatitis is rare. Leukopenia with granulocytopenia has been noted either early or late in the course of therapy. Acute agranulocytosis has not as yet been reported as occurring in the course of therapy with this drug but undoubtedly will occur. Mild or severe acute hemolytic anemias are uncommonly seen. Microscopic or gross hematuria has occurred in about 2.5 per cent of the patients who have received this drug, and anuria with azotemia has been observed. The hematuria and more severe evidence of kidney damage may be due in certain instances to the formation of acetylsulfathiazole crystals and renal calculi which block the renal tubules or even the renal pelves and ureters, but in other patients these toxic manifestations seem to result from a direct toxic reaction of the drug on the renal epithelium. Because of these renal toxic reactions it is important to keep the urinary output above 1,000 cc. in the course of therapy with sulfathiazole.

A curious toxic manifestation which has hitherto been unreported in the course of therapy with sulfanilamide or sulfapyridine, and which has been noted frequently in the course of sulfathiazole therapy, is the injection of the scleras and conjunctivas, which when severe may give the appearance of the disease "pink eye." Mild to severe arthralgia may accompany the fever and rashes which are produced by sulfathiazole.

When fever, rash, hepatitis, granulocytopenia, acute hemolytic anemia, hematuria with oliguria, injection of the scleras and conjunctivas or other serious toxic manifestations occur the drug should be stopped and fluids forced in order that sulfathiazole may be eliminated from the body as rapidly as possible.

As far as is known at the present time, sulfathiazole can be used concurrently with any other drugs, with the possible exception of magnesium sulfate or other saline laxatives. It is not

necessary to try to elminate sulfur-containing foods from the diets of patients who are receiving sulfanilamide, sulfapyridine or sulfathiazole.

*Dosage.*—Sulfathiazole is poorly soluble and hence must be administered by the oral route. Sulfathiazole should not be used in the therapy of any type of meningitis, because the drug does not pass over readily into the spinal fluid.

In the treatment of pneumococcic pneumonia in adults (patients over 14 years of age) the initial dose of sulfathiazole should be 4 Gm., to be followed by 1 Gm. every four hours day and night until the patient's temperature has been normal for seventy-two hours. The drug should then be discontinued. In children ill with pneumococcic pneumonia the initial dose should be based on 0.15 Gm. per kilogram (up to 25 Kg. body weight) and the total daily dose is calculated on the same basis. The total daily dose should be divided into four equal parts and administered at six hour intervals until the temperature has been normal for thirty-six hours. The drug should then be stopped.

It is to be remembered that surgical measures, both supportive and operative, must be used in the treatment of staphylococcic infections in conjunction with sulfathiazole whenever indicated. Surgical drainage of purulent foci must be effected, because while the drug may halt the invasive manifestations of staphylococcic infection it will not by itself cure areas of localized infections, and a flare-up of the infection from such areas is likely to occur if they are not properly drained.

The drug should not be used in the treatment of minor staphylococcic infections such as localized boils and small carbuncles or in mild furunculosis. In large boils or carbuncles, the initial dose for adults should be 4 Gm., followed by 1 Gm. every four hours day and night for from five to seven days. In diffuse staphylococcic cellulitis, lymphangitis or acute osteomyelitis, in adults 4 Gm. should be given as an initial dose, to be followed by doses of 1.5 Gm. every four hours day and night as long as evidence of a spreading infection continues. The dose should then be reduced to 1 Gm. every four hours day and night and continued as indicated. In staphylococcic bacteremia the initial dose for adults should be 4 Gm. followed by 1.5 Gm. every four hours day and night until the temperature has been normal for forty-eight hours. The dose may then be reduced to 1 Gm. to be given every four hours day and night for fourteen days, at which time the dose may be reduced to 0.5 Gm. every four hours day and night to be continued for a minimum of fourteen days. In severe staphylococcic infections in children, the initial dose should be calculated on the basis of 0.2 Gm. per kilogram of body weight (up to 20 Kg. of weight). The total daily dose is calculated on the same basis and should be divided into the six parts, given at four hour intervals day and night until the temperature has been normal for forty-eight hours. Then the dose may be cut by one third and treatment should be continued at this level of dosage for fourteen days, at which time the current dose may be reduced by one half. In staphylococcic bacteremia there is a great possibility that a relapse will occur unless prolonged treatment with the drug is employed. In chronic staphylococcic infections, such as osteomyelitis, not enough information is available to warrant definite instructions as to the use of the drug.

It is very important to control the administration of sulfathiazole by determining its concentration in the blood of patients who are receiving it. In pneumonia, concentrations of from 4 to 6 mg. per hundred cubic centimeters are desirable. In severe or bacteremic staphylococcus infections, concentrations of 7 to 10 mg. per hundred cubic centimeters of the drug in the blood should be sought. These may both be determined by employing Marshall's method (*J. Biol. Chem.* **128**:537 [May] 1939). The recovery of sulfathiazole from the blood is practically quantitative when a 1 to 50 dilution of the blood is used and the determination read in a photoelectric colorimeter. With an ordinary colorimeter and using a 1 to 20 dilution of the blood, the recovery of sulfathiazole is not quantitative and a factor of 15 per cent should be added to the reading obtained. This factor holds for concentrations of from 1 to 10 mg. per hundred cubic centimeters of the drug in the blood.

Sulfathiazole occurs as a white, practically odorless and tasteless crystalline powder. It is soluble in glacial acetic acid and in pyridine, slightly soluble in ethyl, methyl and isopropyl alcohols, very slightly soluble in water, and insoluble in benzene, chloroform, ether, ethyl acetate and ethylene dichloride. It is soluble in dilute mineral acid solutions and alkali metal hydroxide and carbonate solutions; slightly soluble in alkali metal bicarbonate solutions. It is soluble in hot water and in hot ethyl, methyl and isopropyl alcohols; moderately soluble in hot acetone. When sulfathiazole is heated in a capillary tube, slight sintering occurs at from 168 to 175 C., and the substance melts at from 200 to 203.5 C., with slight decomposition. [When the melting point is determined using a micromelting point stage, there may be indicated the presence of two crystalline forms having separate melting points. Crystals melting about 172-173 C. may be observed to undergo a transition in the solid state at this temperature and, if melted, may recrystallize (on scratching or seeding with a crystal having a melting point of 200-203.5 C.) in a form having a melting point of 200-203.5 C.]

Place approximately 0.1 Gm. of sulfathiazole in a small test tube containing a thermometer. Heat the tube cautiously on a sand bath: the material melts, a brown color develops, the product decomposes rapidly at about 230 C. (distinction from sulfanilamide and sulfapyridine), the odor of hydrogen sulfide is evolved, and a stain is produced on a strip of moist lead acetate paper held at the mouth of the tube. Dissolve about 20 mg. of sulfathiazole in 0.25 cc. sodium hydroxide solution and 5 cc. of water; add copper sulfate solution dropwise: with shaking a grayish purple precipitate forms (distinction from sulfapyridine, which yields a green precipitate, and sulfanilamide, which yields a blue solution or precipitate). Boil 0.3 Gm. of sulfathiazole with 3 cc. of glacial acetic acid, cool, add 0.2 cc. of acetic acid anhydride and boil for three minutes. Cool the solution, add 3 cc. of water, mix and allow to stand for ten minutes; filter, wash the precipitate with water and dry at 100 C.: the melting point of the acetyl sulfathiazole obtained is from 265 to 269 C.

Dissolve 0.5 Gm. of sulfathiazole in 25 cc. of hot alcohol: the solution is clear and colorless. Dissolve 1 Gm. of sulfathiazole in 20 cc. of water containing 0.25 Gm. of sodium hydroxide: the solution is clear and colorless. Dissolve 0.5 Gm. of sulfathiazole in 5 cc. of hot dilute hydrochloric acid: the solution is clear and colorless. Cool the acid solution, add 5 cc. of concentrated hydrochloric acid and allow to stand: a feathery white precipitate forms.

Digest 1.5 Gm. of sulfathiazole, accurately weighed, with 75 cc. of water at 70 C. for ten minutes; cool and filter: the saturated aqueous solution of sulfathiazole is neutral or slightly acid ($p_H$ = 5.6 to 6.3) to litmus. To 25 cc. of the filtrate add 5 drops of nitric acid and 1 cc. of silver nitrate solution: the turbidity produced does not exceed that produced in a control test by 0.25 cc. of fiftieth-normal hydrochloric acid. Evaporate another 25 cc. portion of the filtrate to 10 cc., cool, filter, if necessary, and add 0.5 cc. of normal hydrochloric acid and 1 cc. of barium chloride solution: the turbidity produced does not exceed that produced in a control test by 0.1 cc. of one-hundredth normal sulfuric acid.

Incinerate 1 Gm. of sulfathiazole, accurately weighed, in a procelain vessel: the residue amounts to not more than 0.05 per cent. Add to the residue on incineration 1 cc. of hydrochloric acid and 5 drops of nitric acid; evaporate to dryness on the steam bath; warm the residue with 1 cc. of normal hydrochloric acid, add 40 cc. of distilled water, filter and add 10 cc. of freshly prepared hydrogen sulfide solution: the darkening produced is not greater than that produced in a control test made with 0.02 mg. of lead.

A 0.1 Gm. portion of sulfathiazole will pass the test for arsenic given in the U. S. P. XI, page 436.

Dry about 1 Gm. of sulfathiazole, accurately weighed, at 100 C. for five hours: the loss does not exceed 0.5 per cent.

The sulfur content of dried sulfathiazole is not less than 24.7 per cent nor more than 25.3 per cent. The nitrogen content of dried sulfathiazole is not less than 16.2 per cent nor more than 16.6 per cent.

Dissolve about 0.5 Gm. of sulfathiazole, accurately weighed, in 50 cc. of water and 5 cc. concentrated hydrochloric acid; cool to 15 C., and titrate with tenth-molar sodium nitrite solution. The endpoint is the first immediate blue streak obtained when a glass rod dipped into the solution is drawn across a smear of starch-iodide paste on white filter paper. The solution should retain this endpoint for thirty seconds. The use of starch-iodide paste rather than starch-iodide paper is necessary for accurate results. Each cubic centimeter of tenth-molar sodium nitrite corresponds to 0.02553 Gm. of sulfathiazole: the amount of sulfathiazole found corresponds to not less than 99.5 nor more than 101.0 per cent, calculated on the dried basis.

NOTE.—The starch-iodide paste is prepared as follows: Boil 430 cc. of water in a beaker set in an oil bath; add 3 Gm. of potassium iodide dissolved in 15 cc. of water, followed by 7.5 Gm. of zinc chloride dissolved in 30 cc. of water. While the solution is boiling, add, with stirring, a slurry of 20 Gm. of potato starch in 100 cc. of cold water. Continue to boil for two minutes, then cool and store the paste in tightly stoppered bottles. The starch-iodide paste must show a definite blue streak when a glass rod dipped in a solution of 1 cc. of tenth-normal sodium nitrite and 10 cc. hydrochloric acid dissolved in 1 liter of water is drawn across a smear of the paste; otherwise, fresh paste must be prepared.

The tenth-normal sodium nitrite solution must be standardized against pure sulfanilic acid by a similar procedure.

A fact which explains slightly high results is that the endpoint is not as satisfactory when assaying sulfathiazole by the nitrite method as that obtained in the assay of sulfanilamide or sulfapyridine.

**Sulfathiazole-Lederle.**—A brand of sulfathiazole-N. N. R.

Manufactured by the Lederle Laboratories, Pearl River, N. Y. Patents pending. No U. S. trademark.

*Tablets Sulfathiazole-Lederle, 0.5 Gm. (7.7 grains).*

**Sulfathiazole-Maltbie.**—A brand of sulfathiazole-N. N. R.

Manufactured by the Maltbie Chemical Company, Newark, N. J. U. S. patent applied for. No U. S. trademark.

*Tablets Sulfathiazole-Maltbie, 0.5 Gm. (7.7 grains).*

**Sulfathiazole-Merck.**—A brand of sulfathiazole-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. U. S. patent applied for. No U. S. trademark.

*Tablets Sulfathiazole-Merck, 0.5 Gm. (7.7 grains).*

**Sulfathiazole-Squibb.**—A brand of sulfathiazole-N. N. R.

Manufactured by E. R. Squibb & Sons, New Brunswick, N. J. Patent application pending.

*Tablets Sulfathiazole-Squibb, 0.5 Gm. (7.7 grains).*

**Sulfathiazole-Winthrop.**—A brand of sulfathiazole-N. N. R.

Manufactured by the Winthrop Chemical Co., Inc., New York. U. S. patent applied for. No U. S. trademark.

*Tablets Sulfathiazole-Winthrop, 0.5 Gm. (7.72 grains).*

*Tablets Sulfathiazole-Winthrop, 0.25 Gm. (3.86 grains).*

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

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SATURDAY, JANUARY 25, 1941

## THE NATIONAL EMERGENCY AS A PRETEXT FOR COMPULSORY HEALTH INSURANCE

Last week THE JOURNAL commented editorially on a recommendation made by Governor Olson of California to the California legislature that California adopt a system of universal compulsory health insurance. That recommendation was apparently based on inadequate study and revealed a failure to appreciate many factors intimately involved in the recommended scheme for medical care. Now comes a recommendation by Governor Lehman of New York in a special message to the New York legislature on January 14, in part as follows:

> Your legislative commission on medical care and health insurance will report to you at this session. I repeat again that I am very much in sympathy with the principle of health insurance to take care of the medical and hospital needs of those with subnormal incomes. I hope that in the near future such individuals in our state and throughout the nation will be protected against the hazards of illness by a federal insurance system integrated with the federal social security program. I recommend that the report of your committee be given careful consideration.

Governor Lehman's recommendation forecasts a report which is to emanate shortly from the legislative commission on medical care and health insurance. The governor himself, however, notwithstanding some statements in the past, seems to favor compulsory federal sickness insurance.

Significant of the legislative thinking in New York, reflecting as it undoubtedly does the pressures of the health insurance groups, is a statment released January 7 by Justice R. Foster Piper of Erie County, retiring chairman of the special joint legislative committee for revision of the insurance law, of which he has been chairman since its creation in 1937. Justice Foster stated in part:

> In my opinion, if the medical expense indemnity corporations do not fill this need (care of the public's medical service wants) eventually the state of New York must go all the way and provide for health insurance.
>
> If, after a few years, it is found these corporations are not set up and functioning effectively, there appears to be nothing left to do except to establish state health insurance.

This year advocates of measures for health insurance are using the military emergency as added pressure. All sorts of extraneous matters are being plausibly advanced as supplementary to preparedness. There is a drive toward hasty enactment of new proposals into law, without giving them the acid test of argument and evaluation that could reasonably be anticipated in more normal times. Moreover, many agencies that ordinarily could be expected to be vigilant in opposing ill considered legislative proposals will be so engrossed in making workable features of the national defense within their particular domains that they will have neither the time nor the facilities for added attention to medical matters. The psychology engendered by war is already being used to stigmatize unfavorably efforts in opposition to certain proposals that in other, more thoughtful, times would be deemed praiseworthy and in the public interest.

Health insurance proponents begin their arguments with the statement that national defense cannot and will not reach its peak until measures are advanced that will enable the attainment of the optimum in the health of those who will eventually comprise the armed forces. Then they make the same statement for the population in general. The desirability of good health for all cannot be disputed. With careless disregard of minor premises and conclusions the argument continues to the general effect that our present system of medical care is inadequate and cannot produce the optimum in health conditions called for by the emergency. Resort must therefore be had, they insist, to a system of health insurance.

The future will tell how effective such argument will be with the legislatures and with the people. The signs are ominous for the continuation of a high quality of medical care and for respect of the rights of the people in relation to their health. A determined drive is on by health insurance fanatics to capitalize on the opportunity now presented by the emergency. Opposed to them are the forces of scientific professional medicine. Opposed also is the vastness of the funds they seek and the greater need for funds of the military and naval agencies needed in emergency.

But these advocates of health insurance go to extraordinary lengths to attain their ends. Some do not hesitate to place the achievement of their social objectives above the defense needs of the nation.

In Washington State in the last general election in November were a hundred or more initiative proposals which the electorate were called on to pass. One was a so-called "Senior Citizens Grants Act." As far as the ballot title was concerned, the sole basis of the individual voter's information as to what he was passing

on, this measure purported only to grant a monthly income of $40 to persons 65 or over and to provide burial expenses. The measure was adopted by the voters. Hidden away in the measure was section 15, which read:

> In addition to Senior Citizen Grants, the Department shall provide for those eligible medical, dental, surgical, optical, hospital and nursing care by a doctor of recipient's own choosing. . . .

So now in the state of Washington for one part of the population there is state medicine—after a fashion. This measure covers those over 65 years of age. Next will come efforts to reduce the age limit and to include more and more of the population.

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## PERIPHERAL NEURITIS DUE TO SULFONAMIDE COMPOUNDS

The pharmacologic literature on various chronic toxic reactions with sulfonamide derivatives in the experimental animal has been scarce and unsatisfactory; indeed, many physicians believe that at least some of these phenomena cannot be produced experimentally. Thus there has occurred a tendency to try new derivatives clinically before satisfactory pharmacologic evidence has accumulated.

Among the reasons for this attitude is the fact that experiments on the acute toxicity of these drugs have been taken as a standard far too rigidly for the repeated administration of the drugs to man. The toxicity of single doses is not evidence of chronic toxicity. Pharmacologists have seldom given sufficient consideration to experiments involving long-continued administration of remedies. Gradually, however, this dearth of experiments is being rectified.

As most of the experimental work involving the therapeutic action of these drugs has been conducted on mice, rats and rabbits, it is not surprising that these species were the first to be used in "chronic" toxicity experiments. However, the failure of any particular toxic manifestation to appear after long use does not mean that it cannot be produced by experimental methods. It is more apt to mean that it should be looked for in some other species of animal. Until all available species of animals have been studied, one cannot say that any particular symptom of chronic toxicity cannot be produced experimentally.

In the experiments of Bieter, Baker, Beaton, Shaffer and Seery [1] a significant approach has been made on the question of experimental peripheral neuritis. Their confirmation of the pathologic studies of Nelson [2] on sulfanilamide strengthens the claim that the chicken is a good test animal for peripheral neuritis with the sulfonamide group of drugs. Even if the chicken should be shown to be one hundred times more sensitive to this pathologic reaction than man—and as a guess this figure does not seem to be out of proportion at present—this species may serve a useful purpose in helping to determine the comparative safety of a given drug in the series. Up to the present time this has been impossible.

Turning now to the drugs that have been studied by the Minnesota investigators, one can say that the clinical evidence concerning peripheral neuritis following the administration of sulfanilamide and sulfapyridine—the two least harmful of the drugs in their series—is certainly not extensive. Uliron and sulfamethylthiazole appear at present to be capable of producing this injury in man too frequently to warrant their routine clinical use.

The most important question raised by their work concerns sulfathiazole. Their experiments indicate that this drug can produce more injury than either sulfanilamide or sulfapyridine. What does this mean in terms of clinical medicine? Bieter, Baker and their collaborators support their belief that this drug may produce symptoms of injury by reporting what appears to be quite likely a case of peripheral neuritis in man after administration of this drug. True an extremely long period of administration of the drug was used in this case. With certain persons, however, this is not necessarily a procedure to be condemned. In these instances it may be the lesser risk for the patient.

One other point comes to mind in connection with clinical peripheral neuritis: Cottrell [3] has recently shown that apparently normal peripheral nerve trunks in man show definite changes of a degenerative nature which occur with age. In the group of nerves she has studied, namely the median, femoral, sciatic and common peroneal, these changes occur first in the sciatic. Possibly changes of this nature may make a nerve more susceptible to the toxic neurotropic action of these drugs.

The ultimate answer to the various questions concerning peripheral neuritis with the sulfonamide group of drugs requires much more experimental and clinical study. This experimental approach should be continued and extended. Perhaps even more desirably, physicians should watch for this toxic manifestation as well as for all others to be observed with this form of therapy. When all the untoward reactions have been studied thoroughly and reported, the information will be valuable in the chemical approach toward new compounds that possess a minimum of this and other toxic manifestations.

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1. Bieter, R. N.; Baker, A. B.; Beaton, J. G.; Shaffer, J. M., and Seery, T. M.: **A Preliminary Report on the Nervous Injury Produced by Sulfanilamide and Its Derivatives in the Chicken**, in press.

2. Nelson, A. A.: **Histopathological Changes in Hens and Rabbits Following Administration of Sulfanilamide and Sulfanilyl Sulfanilamide (Di-Sulfanilamide)**, Pub. Health Rep. **54**: 106 (Jan. 27) 1939.

3. Cottrell, Lillian: **Histologic Variations with Age in Apparently Normal Peripheral Nerve Trunks**, Arch. Neurol. & Psychiat. **43**: 1138 (June) 1940.

# Current Comment

## HEALTH ACHIEVEMENTS IN WISCONSIN

The State Medical Society of Wisconsin has published a graphic pamphlet entitled "Health Achievements in Wisconsin." The typography and numerous illustrations make the statement especially attractive. The first picture is a map of the United States in which North Dakota, South Dakota and Wisconsin are numbered 1, 2 and 3 in solid black against a white background. Wisconsin was rated by the National Resources Board as the third healthiest state in the United States. The picture of a girl reading comfortably in a hospital bed calls attention to the fact that hospitals are as available in Wisconsin as they are in the state of New York. Pictures of water works, private wells, tourists' cabins, summer resorts, rivers, lakes and packing plants emphasize that Wisconsin protects the public health through the sanitary regulation of hotels, restaurants and barber shops and makes vacationing safe. There are fewer typhoid deaths in Wisconsin than in any other state in the United States. The second section of the pamphlet depicts "Medical Education and Training." Various phases in the life of a medical student are shown in a series of pictures. The third section points out the "Problems on Which Medicine Is Now Working." The state medical society, the state board of health and the industrial commission have done well in bringing so vividly to the front the health achievements in Wisconsin. A brochure of this type will no doubt indicate to the legislators of the state that conditions of health and medical care in Wisconsin are not so abysmally deficient as some proponents of a new order have depicted them.

## MEDICAL CARE FOR INDIGENT IN PENNSYLVANIA

The Medical Society of the State of Pennsylvania has for several years conducted, in cooperation with relief authorities, an extensive system of providing medical care to recipients of varying forms of state public assistance. This plan provides for "free choice, personal relationships, professional management, and fee basis for payment." The demand for professional service has greatly increased since Sept. 15, 1938, but no proportionate increase in the state funds has been made in the meantime. There are more than four thousand Pennsylvania physicians who have entered into an agreement to provide service through this plan. A recent report by Walter F. Donaldson,[1] secretary of the Medical Society of the State of Pennsylvania, says:

> It was commonly claimed that while the total number of persons on direct relief due to unemployment has been materially reduced in Pennsylvania during recent months because of national defense and other sources of increasing employment, the fact remains that the physically handicapped, chronically ill, and persons of low resistance not desirable for reemployment continue their requests for medical service on an increasing scale as the knowledge of the existence of the service and expressions of satisfaction with it continue to spread.

1. Donaldson, W. F.: Officers' Department, Pennsylvania M. J. 44: 495 (Jan.) 1941.

The funds available in the city of Philadelphia, which in 1938 were sufficient to pay a reduced fee schedule in full, by June 1940 met only 31 per cent of the fees.

## CONGRESS ON MEDICAL EDUCATION AND LICENSURE

Elsewhere in THE JOURNAL[1] appears the program of the Congress on Medical Education and Licensure sponsored, since 1905, by the Council on Medical Education and Hospitals of the American Medical Association. In these conferences the Federation of State Medical Boards actively participates. This year special emphasis is placed on medical preparedness as it affects the training of physicians. Other topics to be presented are the adjustment of medical education to social demand, the contribution of liberal education to professional training, the educational purpose of the standard nomenclature of disease, and the education of the Negro physician. Of particular interest to members of licensing boards will be papers dealing with the legal status of physicians and the enforcement of medical practice laws. All who may be interested are invited to attend.

## RADIO INTERFERENCE CAUSED BY DIATHERMY

Standards for reducing interference with radio communications resulting from the use of diathermy apparatus are sorely needed. The Federal Communications Commission recently held an informal engineering conference in Washington with representatives of the medical profession and of the manufacturers of electromedical equipment to consider this subject. The medical profession was officially represented by members of the Council on Physical Therapy of the American Medical Association. In this conference the spokesman for the commission said that the commission recognized the importance of diathermy for the treatment of human ills and reiterated the desire of the commission to cooperate with the medical profession and with the manufacturers. At the Inter-American Radio Communication Conference, Santiago, Chile, in 1940 it was decided that countries in the Western Hemisphere "shall adopt measures to suppress or alleviate as much as possible interference caused by apparatus or equipment which may generate or radiate radiofrequency currents capable of interfering with or adversely affecting the reception of radio transmissions." One method to eliminate interference is to design diathermy apparatus to operate on definite frequencies and allocate these channels for this purpose only. The spokesman for the manufacturers asked for the allocation of three bands corresponding approximately to 23, 11.5 and 7.67 meters, the width of the bands to be comparable to ten broadcast channels at 23 and 7.6 meters and forty channels at 11.5 meters or sixty broadcast channels in all. Representatives of the commission felt that this request would not be granted because it required the setting aside of too many valuable channels of communication. The commission urged rather that apparatus be manufactured which would operate on one channel of communication without exten-

1. Organization Section, p. 319.

sive deviation and also satisfy the demands for diathermy. Some manufacturers believed that this probably could be achieved but at a prohibitive cost. Others did not believe it could be done. Indeed, the manufacturers pointed out that diathermy equipment is operated by physicians and technicians who are not trained radio engineers and hence the users would not be in a position to make the necessary adjustments to maintain frequency stability as in radio broadcasting. Some manufacturers estimated that diathermy equipment which would meet the more rigid requirements would cost between $1,000 and $1,500, not to mention service expense. Naturally representatives of the medical profession voiced their objection to the increase in the cost of electromedical apparatus. The problem will have further study. A committee was appointed to look into engineering practices and circuit design costs and to report back to the group at a future conference.

## PUBLIC HEALTH FELLOWSHIPS AVAILABLE TO QUALIFIED APPLICANTS FROM OTHER AMERICAN REPUBLICS

Pursuant to federal statutory authority, the Surgeon General of the United States Public Health Service has announced [1] that, to promote mutual aid and advancement in protecting the public health of the American republics and to bring about closer and more effective relationships between these republics, fellowships in the sciences related to public health are now available in the United States to qualified applicants from our sister republics. These fellowships will be awarded, after application through regular diplomatic channels, by the Surgeon General, on recommendation of the director of the Pan American Sanitary Bureau and with the approval of the Secretary of State of the United States. Applicants who qualify for selection for these fellowships must be (1) bona fide citizens of any one of the American republics other than the United States, (2) in good physical condition as evidenced by a certificate of medical examination issued by a physician within sixty days of the date of application, (3) able to speak, read, write and understand the English language and (4) of good moral character and possess intellectual ability and suitable personal qualities, and have successfully completed academic professional training in a recognized school in any one of the branches related to the science of public health, including, among others, medicine, dentistry, pharmacy, sanitary engineering, nursing, vital statistics, chemistry and bacteriology. These fellowships are to be of the training in research type. They may comprise (1) advanced scientific research in a recognized organization, university or other institution in the United States or (2) postgraduate work in an approved college or university, or internship and/or nonresident work in an approved hospital or other institution for the treatment, care or prevention of disease in the United States. The fellowships will be awarded for periods of varying length not exceeding one school year or twelve months of actual studies or research, but they may be extended on recommendation of the director of the Pan American Sanitary Bureau. Successful applicants, on the recommendation of the director of the bureau, will be entitled to (1) reimbursement for necessary transportation expenses, (2) a per diem in lieu of subsistence allowance which shall not exceed $5 a day while inside the United States and (3) other incidental expenses, including enrolment fees, tuition, medical and infirmary fees, laboratory fees, cost of textbooks and rental of equipment, payable to the institution, person or firm rendering or furnishing such services or supplies. The education of physicians and scientists from our sister American republics will do as much as any other project to earn for us friendship, respect and understanding. Even a small expenditure for such purposes may earn a vast return.

1. Federal Register 5: 5238 (Dec. 24) 1940.

## SAMPLE RACKETEERS

Just received is a copy of a letter written by one L. M. Wilson to a physician in Pennsylvania, suggesting that this physician write a letter to a dozen different manufacturers asking each of them to send him samples in large quantities to be used by his family. Apparently L. M. Wilson hopes some day soon to call on the doctor and to collect from him all these samples. Thus L. M. Wilson writes:

> Dear Doctor: I am enclosing a list of a few items that I can buy from you and pay a fairly good price if you can obtain them. These items are all put out by large companies and will send this material indefinitely if not asked for too often i. e. once every month or 6 weeks. Will stop in to see you in about a month—as you should have them all by then if they are sent for immediately. Sample letter— Dear Sirs: I would like to request a supply of your product, —— ——, for use in my own personal family—at your earliest convenience. Could you also enclose descriptive literature?

With this naive proposal is a list of all the different preparations to be requested, some apparently for use in the family, some for use by the doctor himself, as, for instance, for prostatic hypertrophy and for glandular stimulation, and others to be used in doing clinical research. Any physician who would cooperate in a performance of this type is participating in a distinctly unethical procedure and is lending himself to what is essentially a fraud.

## PERIODICAL HONORS DR. HOWARD LILIENTHAL

The January-February issue of the *Journal of the Mount Sinai Hospital* is dedicated to Dr. Howard Lilienthal, the eminent surgeon, on the occasion of his eightieth birthday. In the foreword, written by Dr. Evarts A. Graham, it is pointed out that Dr. Lilienthal was one of the first to urge cholecystectomy as a more common operation than the then more used cholecystostomy. It was, however, the field of the thoracic cavity that called forth Lilienthal's most brilliant work. He published reports of the first considerable series of cases of lobectomy for bronchiectasis. His book Thoracic Surgery, published nearly twenty years ago, is still a classic. This number of the *Journal of the Mount Sinai Hospital,* dedicated by some seventy-five of Lilienthal's friends, associates and pupils, contains nearly fifty articles covering a wide range of medical subjects.

# MEDICAL PREPAREDNESS

***In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.***

## NEW MEDICAL DIRECTOR FOR SELECTIVE SERVICE

According to the Washington, D. C., *Evening Star*, Col. Leonard G. Rowntree, Medical Reserve Corps, has been appointed medical director of the Selective Service System, to succeed Lieut. Col. Charles B. Spruit, U. S. Army, who has been assigned to the War Department general staff. Colonel Rowntree was formerly associate professor of medicine at Johns Hopkins University School of Medicine, Baltimore, and for many years was professor of medicine at the University of Minnesota and chief of the medical division of the Mayo Foundation. He is a past president of the American Society for Clinical Investigation and of the Association for the Study of Internal Secretions. During the first World War he served in France as an executive officer of the Air Service Research Laboratories.

## A SURVEY OF NURSES

A questionnaire has been prepared to be sent to all registered nurses in the United States and its territories. The information assembled will be analyzed by the U. S. Public Health Service and the results made available to any agency having need for such facts. These preparations were disclosed by Surgeon General Parran at a conference in Washington, D. C., January 10. The purpose of the registration, Dr. Parran said, is to determine the number of these professional people, their availability for military or civil duty, and their special attainments. Other speakers at the conference were Miss Julia Stimson, chairman of the Nursing Council on National Defense; Miss Mary Beard, director, Nursing Service, American Red Cross; Miss Mary Roberts, editor of the *American Journal of Nursing*, and Miss Annabelle Peterson, president of the District of Columbia Graduate Nurses' Association.

## CONFERENCE ON PSYCHIATRY IN MILITARY MEDICINE

A symposium on "Psychiatric Aspects of Military Medicine" will be held in the psychiatric division of the Bellevue Hospital at the foot of East Thirtieth Street, New York, February 4, under the auspices of the 205th General Hospital (RAL) and the 4th Hospital Center (RAI). The speakers will include:

Dr. Karl M. Bowman, Psychiatric Examinations in the Armed Forces.
Dr. Samuel Adams Cohen, The Army Medical Officer Looks at Psychiatry.
Dr. Abram Kardiner, Neuroses of War.
Dr. Sandor Rado, The War of Nerves.
Dr. Edwin G. Zabriskie, The Psychoses of the Last War.

Discussion will be led by Drs. Francis M. Shockley, Clarence P. Oberndorf and George E. Daniels. Dr. Leo L. Orenstein will make some introductory remarks and Dr. Joseph Haas will close the program.

## RED CROSS-HARVARD HOSPITAL AND PUBLIC HEALTH UNIT IN ENGLAND

The American Red Cross and Harvard University have joined forces in providing a hospital and a public health unit which will cooperate in the study and treatment in England of communicable disease under wartime conditions.

The American Red Cross is constructing in this country a one hundred and twenty-six bed "siege" hospital to be set up next month in England. The combined undertaking, consisting of seventy-five American doctors, Red Cross nurses and laboratory technicians, is scheduled to begin operations on completion of the twenty-two building hospital.

Dr. John E. Gordon, professor of preventive medicine and epidemiology in the Harvard Medical School, who will be general director of the combined undertaking, is enroute to England, accompanied by Dr. Paul B. Beeson of Wooster, Ohio, resident physician of the Peter Bent Brigham Hospital and assistant in medicine at the Harvard Medical School, who will be chief physician of the unit.

Preliminary arrangements for the study were made last August, when Dr. Gordon went to London with Dr. John R. Mote, assistant in preventive medicine and epidemiology at Harvard Medical School. Dr. Mote, who has remained in London handling details with the Ministry of Health, will serve as head bacteriologist when the study gets under way.

Dr. Gerald F. Houser, assistant director of the Massachusetts General Hospital, has been named as superintendent of the hospital and will go to England later this month.

The Red Cross-Harvard Hospital will consist of twenty-two buildings of a design developed for modern warfare and constructed of prefabricated sections of five ply building board sandwiched between fire resistant sheets. They will be bolted in a structural steel framework and camouflaged to match the surrounding terrain. At the end of each building there will be a vestibule arrangement to allow doctors and nurses to enter and leave without light escaping.

Other members of the staff named by Harvard are Dr. Dean S. Fleming of South Minneapolis, Minn., Minnesota state fellow of public health at Harvard; Dr. William L. Hawley, Birmingham, Ala., who has been serving as medical house officer at the Peter Bent Brigham Hospital; Dr. Thomas F. McNair Scott, bacteriologist, research professor of pediatrics at the University of Pennsylvania; Dr. Alex J. Steigman, house officer of Children's Hospital at Philadelphia, and Miss Eleanor Hathaway, Andover, Mass., Miss Elizabeth B. Jackson, Boston, Mrs. Edelmira Hendee, Newburgh, N. Y., technicians, and Mr. Chester A. Whitney, Weymouth, Mass., roentgen ray and photographic technician. The secretary of the unit will be Miss Mary Alice Jaqua, secretary of the Grant Study, Harvard University.

A contingent of fifty Red Cross nurses will be headed by Miss Gertrude Madley of Detroit, chief nurse; Miss Elisabeth Phillips, New York, associate chief nurse in charge of public health nursing operations, and Miss Alice Olson of Milwaukee, assistant chief nurse. The Red Cross will be responsible for the general management of the hospital.

Dr. Gordon said that a site has been selected, in cooperation with the British authorities, for the establishment of a one hundred bed hut type of hospital, designed for communicable disease purposes. The site is ideal for the purposes of the unit. It is in a rural area. The project presents special opportunities for experimentation of the greatest interest. It provides for the coordination of the field, laboratory and hospital phases of epidemiologic work under a single head.

## CLASS OF AVIATION MEDICAL EXAMINERS AT RANDOLPH FIELD

A six weeks routine course of instruction to qualify medical officers for duty as aviation medical examiners began at the School of Aviation Medicine, Randolph Field, Texas, January 2. The names of the officers enrolled and the stations to which they are assigned follow:

MEDICAL RESERVE CORPS

ARNOLDI, Louis B., 1st Lieut., Maxwell Field, Ala.
BACH, Leo F., Captain, Air Corps Training Detachment, Hemet, Calif.
BAERS, Harry, 1st Lieut., Battalion Dispensary, 29th Field Artillery Battalion, Fort Benning, Ga.
BENNETT, William Horace, 1st Lieut., Eglin Field, Valpariso, Fla.
BROWN, Thomas P., 1st Lieut., Chicago School of Aeronautics, Glenview, Ill.
CHAMPION, Walton T., 1st Lieut., Fort Riley, Kan.
COGAN, Leo J., Captain, Chanute Field, Ill.
COLVIN, Paul V., 1st Lieut., Kelly Field, Texas.
CUMMING, Richard C., Captain, Air Corps Training Detachment, Lakeland, Fla.
CURTIS, Morris W., Captain, Langley Field, Va.
DAVIS, Elmer L., Captain, Brooks Field, Texas.
DEUTSCH, Albert L., 1st Lieut., Savannah Air Base, Savannah, Ga.
DURHAM, Milton W., 1st Lieut., Gray Field, Fort Lewis, Wash.
ERICKSON, John W., 1st Lieut., Randolph Field, Texas.
ERSHLER, Irving, 1st Lieut., Randolph Field, Texas.
GILMORE, John E., 1st Lieut., March Field, Calif.
GUMPORT, Stephen L., 1st Lieut., Boston Airport, Boston.
HOMAN, James B., 1st Lieut., Fort Eustis, Va.
KAPLAN, Albert J., 1st Lieut., Fort Ethan Allen, Vt.
LEICHTER, Martin, 1st Lieut., Moffett Field, Calif.
LIPPMAN, Nathan L., 1st Lieut., Langley Field, Va.
McREE, Walter E., 1st Lieut., Randolph Field, Texas.
MATTHIS, Austin W., Captain, Fort Douglas, Utah.
NELSON, Robert B., Jr., 1st Lieut., Selfridge Field, Mich.
NOELL, Livingston P., 1st Lieut., Brooks Field, Texas.
PAPKIN, George, 1st Lieut., Hamilton Field, Calif.
PATTERSON, Fred L., 1st Lieut., Spartan School of Aeronautics, Tulsa, Okla.
POHL, Robert Leo, 1st Lieut., Air Base, Spokane, Wash.
SANDY, William A., Captain, Chanute Field, Ill.
SCHNUR, Sidney, Captain, Fort Sam Houston, Texas.
SKOW, George D., 1st Lieut., Patterson Field, Ohio.
STARK, Ray G., 1st Lieut., Scott Field, Ill.
THOMAS, Henry S., 1st Lieut., March Field, Calif.
WADDELL, Otto J., 1st Lieut., Randolph Field, Texas.
WAGNER, Alphonse J., 1st Lieut., Fort Sheridan, Ill.
WHITE, Raymond L., 1st Lieut., Allan Hancock College of Aeronautics, Santa Maria, Calif.
WRIGHT, Jack M., 1st Lieut., Spartan School of Aeronautics, Tulsa, Okla.

NATIONAL GUARD

BROOKE, James W., 1st Lieut., Wisconsin National Guard, Wisconsin General Hospital, Madison, Wis.
COGLAND, John L., Captain, Connecticut National Guard, Hartford, Conn.
HAMMOND, James H., Captain, Oklahoma National Guard, Fort Sill, Okla.
LAGERQUIST, Howard D., Captain, Illinois National Guard, Chicago.
PATTERSON, Robert A., 1st Lieut., Michigan National Guard, 107th Medical Regiment, Camp Beauregard, La.
PATTERSON, Robert C., 1st Lieut., South Carolina National Guard, Columbia, S. C.
THOMAS, Ramsay Berry, 1st Lieut., Maryland National Guard, Baltimore.

MEDICAL CORPS

SELLARDS, Howard E., Captain, Fort McClellan, Ala.
STEVENSON, Ralph T., Captain, Barksdale Field, La.

A class of thirty enlisted men of the Medical Department at the same time began a six weeks course of instruction to qualify them as enlisted specialists.

The School of Aviation Medicine is an activity of the Gulf Coast Air Corps Training Center and, in addition to the resident courses, conducts throughout the year correspondence courses.

The Commandant of the School of Aviation Medicine is Col. Fabian L. Pratt, Medical Corps, and the Adjutant is Major W. Harvey Kernan, Medical Administrative Corps.

## FIRST AID TRAINING AS DEFENSE MEASURE

The American Red Cross is cooperating with the Civilian Conservation Corps in providing first aid training for all enrollees in a program that was to begin January 1. The plan is to assign supervisors to each of the nine CCC corps areas throughout the country. Members of the national staff of the Red Cross will train about three thousand instructors, who in turn will conduct classes in the fifteen hundred camps for three hundred thousand CCC enrollees.

First aid training for members of combat crews of fighting planes has been inaugurated at March Field, Calif., in the Thirty-Eighth Reconnaissance Squadron. Twenty-five men took the first course and, as a result of this pioneer effort, other organizations on the post have asked for instruction, the Red Cross reported. In addition, it is planned to provide training for officers as well as enlisted members of the crews.

## THE RED CROSS MOBILIZES NURSES

The American Red Cross Nursing Service is conducting an intensive mobilization beginning the latter part of January and continuing about six weeks. The minimum goal is to enroll 10,000 new members in the "First Reserve." The First Reserve now has 18,000 members, and it is expected that between 3,000 and 4,000 will be called for duty by June 30. Nurses who enroll must agree to serve with the Army or Navy in time of national emergency. Those enrolled must be under 40 years old, single, physically fit, graduates of high school and accredited schools of nursing and members of the American Nurses Association. Although plans have been made to get in touch with every nurse personally, some inadvertently may be passed over, an announcement states. Any registered nurse who believes her qualifications meet the requirements and who has not been asked to enroll is requested to get in touch with the local committee or write directly to the American Red Cross Nursing Service, Washington, D. C.

## NAVY MEDICAL MEETING

Drs. Charles F. Behrens and Robert E. Duncan, both commanders, medical corps, U. S. Navy, addressed a meeting of the medical and dental officers of the navy on duty in the District of Columbia and vicinity, December 2, on "Navy Procedure for Photo-Roentgen Chest Surveys." The meeting January 6 was addressed by Drs. Charles Armstrong and John W. Oliphant, both of the U. S. Public Health Service, on "Recent Advances in the Epidemiology of Acute Anterior Poliomyelitis and Influenza."

## PHYSICAL DEFECTS AMONG DRAFTED MEN IN WORLD WAR

The United States Public Health Service has reanalyzed certain results of the medical findings pertaining to the prevalence of defects for the World War draft of 1917-1918.

Twenty-one per cent were rejected for military service, 31 per cent were classified as not available for general military service (including the rejections) and 52 per cent had one or more recorded defects.

These figures for the last war were summarized by Rollo H. Britten, senior statistician and George St. J. Perrott, chief, Division of Public Health Methods, Public Health Service (*Public Health Reports*, January 10).

"On the basis of the World War draft of 1917-1918, one might expect that, to meet the quota of 800,000 inducted men by July 1, 1941, 1,200,000 would have to be examined and thus that about 400,000 would not be available for general military service," the co-authors stated.

*Defects per Thousand Total Drafted Men in 1917-1918*

| | |
|---|---|
| Orthopedic impairments | 213.16 |
| Eye defects | 61.01 |
| Cardiovascular-renal diseases | 50.20 |
| Underweight | 31.14 |
| Hernia and inguinal rings | 55.36 |
| Tuberculosis (all forms) actual or suspected | 24.74 |
| Defective or deficient teeth | 26.27 |
| Nervous or mental diseases | 24.53 |
| Ear defects | 15.45 |
| Venereal diseases | 46.77 |
| Varicose veins, varicocele | 8.75 |
| Goiter | 11.38 |
| Hypertrophic tonsillitis | 33.77 |
| Arthritis and allied disorders | 3.48 |
| Asthma | 2.33 |
| Other diseases or defects | 53.56 |
| All diseases or defects | 661.94 |

## ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY

### WAR DEPARTMENT

The following additional medical reserve corps officers had been ordered to active duty by direction of the War Department, Washington, D. C., up to January 10:

ALLISON, Ray Leonard, Captain, Los Angeles.
ASHMAN, Philip, 1st Lieut., Vintondale, Pa.
ABERNETHY, Lynn Dunlap, 1st Lieut., Holly Springs, Miss.
COMSTOCK, Jack Arthur, 1st Lieut., Boulder, Colo.
CUTTS, Francis William, 1st Lieut., Ventura, Calif.
DICKSON, Douglas Dwight, 1st Lieut., Piedmont, Calif.
FRENCH, Edward Brendan, 1st Lieut., Hyde Park, Vt.
GORDON, Devitt Lawrence, 1st Lieut., Detroit.
GROS, Hubert, 1st Lieut., Delphi, Ind.
GUMINER, Stanley Herbert, 1st Lieut., Chicago.
HARRIS, Sidney, 1st Lieut., Roselle, N. J.
KAPLAN, Louis, 1st Lieut., Philadelphia.
McKEE, Claude Worth, 1st Lieut., Pittsburgh.
MORGAN, Edward Shelley, 1st Lieut., Pendleton, Ore.
ORR, Robert Alexander, 1st Lieut., Mayfield, Ky.
PECK, Samuel Glen, 1st Lieut., Santa Ana, Calif.
PLOTZ, Harry, Lieut. Col., Brooklyn.
SHOENFELT, James Whitaker, Jr., 1st Lieut., Altoona, Pa.
SMITH, George Yale, 1st Lieut., Brooklyn.
ST. CLAIR, Alexander Armstrong, 1st Lieut., Bluefield, W. Va.
SWITZER, Ralph Eugene, 1st Lieut., Haybro, Colo.

#### Orders Revoked

Orders on the following officer reported in letter to this office dated Dec. 23, 1940, have been revoked:

AUSHERMAN, Howard Milton, 1st Lieut., Chattanooga, Tenn.

### FIRST CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty with the regular army by the Commanding General, First Corps Area, since January 3. The First Corps Area comprises the states of Maine, Vermont, New Hampshire, Rhode Island, Massachusetts and Connecticut.

CHAMP, Anthony M., Major, Brockton, Mass., Fort Devens, Mass.
BATCHELDER, Hollis G., Colonel, Dedham, Mass., Governor's Island, N. Y.
BLOOMBERGH, John H., Lieut., Chestnut Hill, Mass., Camp Edwards, Falmouth, Mass.
FOGG, Allston H., Major, Burlington, Vt., Camp Edwards, Falmouth, Mass.
GURWITZ, Jack, 1st Lieut., Brookline, Mass., Camp Edwards, Falmouth, Mass.
HALL, Leonard J., 1st Lieut., Lowell, Mass., Fort Devens, Mass.
MATTERA, Vincent J., 1st Lieut., Providence, R. I., Fort Devens, Mass.
MENZIES, Gordon E., Captain, Wickford, R. I., Port Adams, R. I.
MORIARTY, Daniel J., 1st Lieut., Waitsfield, Vt., Fort Ethan Allen, Vt.
SKRECZKO, Charles K., Lieut., Shelton, Conn., Carlisle Barracks, Pa.
SPIRA, Bertram, Lieut., Worcester, Mass., Camp Edwards, Falmouth, Mass.
TRASK, Burton W., 1st Lieut., Augusta, Maine, Camp Edwards, Falmouth, Mass.

#### Orders Revoked

The following medical reserve corps officers have had their orders revoked:

DENNING, Walter S., 1st Lieut., Brookline, Mass.
McIVER, Frederick D., Captain, Orleans, Vt.
PHILLIPS, Robert T., Captain, Portland, Maine.
ROZEN, Alan A., 1st Lieut., New Haven, Conn.
SHAPIRO, Philip, 1st Lieut., Northampton, Mass.
SIMARD, Louis B., 1st Lieut., Haverhill, Mass.
WILLARD, Paul C., 1st Lieut., Montpelier, Vt.

### SECOND CORPS AREA

The following additional medical reserve corps officers had been ordered to active duty by the Commanding General, Second Corps Area, up to January 10, 1941. The Second Corps Area comprises the states of New York, New Jersey and Delaware.

ALBRECHT, Henry F., Jr., Captain, Troy, N. Y., Madison Barracks, N. Y., 1st Military Area.
ALDEN, Carlos C., 1st Lieut., Buffalo, Fort Niagara, N. Y., 1st Military Area.
AYER, Guy D., 1st Lieut., Cooperstown, N. Y., Fort Devens, Mass., 1st Military Area.
BAYER, Eric, 1st Lieut., Englewood, N. J., Fort Ontario, N. Y., 3d Military Area.
BEDRICK, John J., 1st Lieut., Bayonne, N. J., Fort Dix, N. J., 3d Military Area.
BRUNDAGE, Frank E., Lieut. Col., Buffalo, Fort Niagara, N. Y., 1st Military Area.
CATALANO, Russell J., 1st Lieut., Buffalo, Fort Niagara, N. Y., 1st Military Area.
CHIARULLI, Eugene E., 1st Lieut., Syracuse, N. Y., Fort Ontario, N. Y., 1st Military Area.
CUNNINGHAM, Joel B., 1st Lieut., Camden, N. J., Fort Dix, N. J., 3d Military Area.
DANFORTH, Edward P., Captain, Sidney, N. Y., Carlisle Barracks, Pa., 1st Military Area.
DREIZIN, David H., 1st Lieut., Passaic, N. J., Carlisle Barracks, Pa., 3d Military Area.
FIELDING, Robert T., 1st Lieut., Plainfield, N. J., State Armory, Newark, N. J., 3d Military Area.
FISHER, Hyman B., 1st Lieut., New York, Fort Banks, Mass., 2d Military Area.
FRANKEL, Henry, Captain, West New York, N. J., Fort Devens, Mass., 3d Military Area.
FRATANTUONO, M. J., 1st Lieut., Newark, N. J., State Armory, Newark, N. J., 3d Military Area.
GOLDSMITH, Morris, 1st Lieut., Brooklyn, Camp Edwards, Mass., 2d Military Area.
GOLDSTEIN, Sol R., Captain, Rochester, N. Y., Fort Ontario, N. Y., 1st Military Area.

GOODMAN, Kenneth, 1st Lieut., East Orange, N. J., Carlisle Barracks, Pa., 3d Military Area.
GLADSTONE, Albert L., 1st Lieut., Paramus, N. J., Fort Dix, N. J., 3d Military Area.
GREENFIELD, Herbert, 1st Lieut., Newark, N. J., Fort Dix, N. J., 3d Military Area.
GUSTAFSON, Einar G., 1st Lieut., East Elmhurst, L. I., N. Y., Fort Hancock, N. J., 2d Military Area.
HEMINWAY, Norman L., 1st Lieut., Somerville, N. J., Fort Williams, Maine, 3d Military Area.
HOFFMAN, Sidney, 1st Lieut., Brooklyn, Fort Hamilton, N. Y., 2d Military Area.
HOPKINS, Charles E. R., 1st Lieut., Brooklyn, Camp Upton, N. Y., 2d Military Area.
INSABELLA, John, 1st Lieut., Newark, N. J., Carlisle Barracks, Pa., 3d Military Area.
KNITZER, Carl, 1st Lieut., Brooklyn, Carlisle Barracks, Pa., 2d Military Area.
KRAWCZYK, Joseph F., 1st Lieut., Buffalo, Fort Niagara, N. Y., 1st Military Area.
Le BELL, Harold, 1st Lieut., New York, Carlisle Barracks, Pa., 2d Military Area.
LINEHAN, Robert J., 1st Lieut., Binghamton, N. Y., Fort Ontario, N. Y., 1st Military Area.
LIPSHUTZ, Daniel M., 1st Lieut., Brooklyn, Camp Upton, N. Y., 3d Military Area.
LONG, Elias E., 1st Lieut., Long Branch, N. J., Fort Williams, Maine, 3d Military Area.
LYNCH, Edward T., 1st Lieut., Elizabeth, N. J., State Armory, Newark, N. J., 3d Military Area.
MASLANSKY, Lawrence, 1st Lieut., New York, Carlisle Barracks, Pa., 2d Military Area.
McMAHON, Jeremiah J., 1st Lieut., Brooklyn, Governors Island, N. Y., 2d Military Area.
MESSINA, Thomas, 1st Lieut., East Orange, N. J., State Armory, Newark, N. J., 3d Military Area.
MILLIGAN, Paul R., 1st Lieut., Orange, N. J., State Armory, Newark, N. J., 3d Military Area.
O'BRIEN, John J., 1st Lieut., Flushing, N. Y., Fort Jay, N. Y., 2d Military Area.
ORRIS, Harold J., Captain, Hill Side, N. J., Fort Monmouth, N. J., 3d Military Area.
PARIS, William, 1st Lieut., Paterson, N. J., Fort Dupont, Del., 3d Military Area.
PAYES, Leon J., 1st Lieut., Binghamton, N. Y., Fort Ontario, N. Y., 1st Military Area.
PERROTTA, Anthony J., 1st Lieut., Red Bank, N. J., Fort Monmouth, N. J., 3d Military Area.
PICCIOTTI, Joseph D., 1st Lieut., Rochester, N. Y., Fort Ontario, N. Y., 1st Military Area.
ROMANO, Patrick J., 1st Lieut., Orange, N. J., State Armory, Newark, N. J., 3d Military Area.
ROSS, Edward, 1st Lieut., Brooklyn, Fort Hancock, N. J., 2d Military Area.
SAMUELS, Sol L., 1st Lieut., Plainfield, N. J., State Armory, Newark, N. J., 3d Military Area.
SCHULTZ, Leo P., 1st Lieut., Jersey City, N. J., Carlisle Barracks, Pa., 3d Military Area.
SIMPSON, David B., Captain, Bayonne, N. J., Fort Devens, Mass., 3d Military Area.
SHANNON, William F., 1st Lieut., Bellmore, L. I., N. Y., Carlisle Barracks, Pa., 2d Military Area.
STATMAN, Bernhardt J., 1st Lieut., Newark, N. J., Carlisle Barracks, Pa., 3d Military Area.
TIRRELL, Chester M., 1st Lieut., Orange, N. J., State Armory, Newark, N. J., 3d Military Area.
VENET, Louis, 1st Lieut., New York, Fort Jay, N. Y., 2d Military Area.
WOLOWITZ, Harry B., Major, Hackensack, N. J., Carlisle Barracks, Pa., 3d Military Area.
ZUCKER, Isadore, 1st Lieut., Newark, N. J., Fort Dix, N. J., 3d Military Area.

## FOURTH CORPS AREA

The following additional officers in the medical reserve corps have been ordered to active duty by the Commanding General of the Fourth Corps Area since January 3.

The Fourth Corps Area comprises the states of Tennessee, North Carolina, South Carolina, Alabama, Georgia, Mississippi, Florida and Louisiana.

HATCHER, Milford B., 1st Lieut., Macon, Ga., Fort McClellan, Ala.
KEMP, Paul S., 1st Lieut., Macon, Ga., Fort McClellan, Ala.
MATHIAS, Marion L., 1st Lieut., Charleston, S. C., Fort Bragg, N. C.
MICHEL, Marshall L., 1st Lieut., New Orleans, Fort Bragg, N. C.
PREVO, Samuel B., 1st Lieut., Memphis, Tenn., Fort Bragg, N. C.

### Orders Revoked

The following officers previously reported have been relieved from duty or orders revoked:

BLEICH, Jack K., Captain, Atlanta, Ga.
BUCKLEY, Madison H., 1st Lieut., Martin, Tenn.
DE PRIEST, Frederick E., 1st Lieut., Coushatta, La.
DE RAMUS, William H., 1st Lieut., Selma, Ala.
FITZGERALD, Charles E., 1st Lieut., Farmville, N. C.
GARY, Robert E., 1st Lieut., Tuscumbia, Ala.
KAPLAN, Saul H., 1st Lieut., Miami Beach, Fla.
LAIRD, Earl L., 1st Lieut., Union, Miss.
SHAW, Clarence, 1st Lieut., Chattanooga, Tenn.
TREHERNE, Alfred J., Captain, Atmore, Ala.

## SIXTH CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Sixth Corps Area, up to January 10. The Sixth Corps Area comprises the states of Michigan, Illinois and Wisconsin.

ABRAMS, Benjamin, 1st Lieut., Chicago, Reception Center, Fort Custer, Mich.
BLUEFARB, Samuel M., 1st Lieut., Chicago Replacement Center, Camp Grant, Ill.
BRENNER, Frank T., Captain, Cadillac, Mich., Puerto Rican Department.
BROWN, Ira, Captain, Chicago, Station Hospital, Camp Grant, Ill.
COUSENS, Marshall A., 1st Lieut., Chicago, Camp Grant, Ill.
ENDRES, Fred C., Captain, Peoria Heights, Ill., Fort Knox, Ky.
FARMER, David K., 1st Lieut., Broadlands, Ill., Fort Knox, Ky.
FOX, William W., Captain, Lincoln, Ill., Fort Sheridan, Ill.
FRIEDMAN, DAVID, Captain, Madison, Ill., 12th Cavalry, Fort Brown, Texas.
GAZDA, Mace, 1st Lieut., Chicago, Fort Knox, Ky.
GOODMAN, Paul P., 1st Lieut., Milwaukee, 5th Medical Battalion, Fort Knox, Ky.
GORAN, Joseph R., 1st Lieut., Erie, Ill., Fort Knox, Ky.
GORDON, Benjamin F., 1st Lieut., Newago, Mich., 5th Medical Battalion, Fort Knox, Ky.
GORELICK, Harry S., 1st Lieut., Detroit, Station Hospital, Camp Grant, Ill.
GRANDONE, Joseph J., Captain, Gillespie, Ill., Fort Sheridan, Ill.
GREENSPAHN, Gerald M., 1st Lieut., Chicago, 5th Medical Battalion, Fort Knox, Ky.
GREER, Richard H., 1st Lieut., Northport, Mich., 1st Medical Square, Fort Bliss, Texas.
HELM, Standiford, 1st Lieut., Evanston, Ill., Camp Livingston, La.
HELMS, Jacob, Captain, Vanderbilt, Mich., Headquarters Fifth Army Corps.
HURWITZ, Paul, 1st Lieut., Chicago, Station Hospital, Camp Grant, Ill.
JACOBSON, Herman A., Captain, Chicago, Station Hospital, Camp Grant, Ill.
KADIN, Maurice, 1st Lieut., Calumet, Mich., Station Hospital, Camp Grant, Ill.
KATZ, Charles, 1st Lieut., Chicago, Station Hospital, Camp Grant, Ill.
KERR, Charles R., Major, Chenoa, Ill., 4th Medical Supply Depot, Fort Sam Houston, Texas.
KOEPP, Charles E., 1st Lieut., Marinette, Wis., Fort Knox, Ky.
KUEHL, Frederick O., 1st Lieut., Green Bay, Wis., Fort Knox, Ky.
LERNER, Harry A., 1st Lieut., Chicago, 50th Signal Battalion, Fort Sheridan, Ill.
LANGE, Howard L., Captain, Belleville, Ill., Fort Knox, Ky.
LANTING, Roelof, 1st Lieut., Gladwin, Mich., Camp Livingston, La.
LEWIS, Robert M., 1st Lieut., Evanston, Ill., Reception Center, Fort Custer, Mich.
LEWY, Robert B., Captain, Chicago, General Dispensary, U. S. Army, Chicago.
MANTELL, Bernard, 1st Lieut., Chicago, 1st Medical Squadron, Fort Bliss, Texas.
MARCUS, Daniel B., 1st Lieut., Detroit, Station Hospital, Camp Grant, Ill.
McKINLEY, Hugh A., Captain, Highland Park, Ill., Station Hospital, Fort Sheridan, Ill.
MELTZER, Herman L., Captain, Clinton, Ill., Station Hospital, Camp Grant, Ill.
MILLIS, Jack W., 1st Lieut., Chicago, Reception Center, Fort Custer, Mich.
O'FARRELL, Patrick F., Captain, Mount Olive, Ill., Fort Sheridan, Ill.
OVITZ, John W., Jr., 1st Lieut., Sycamore, Ill., Station Hospital, Camp Grant, Ill.
PHELPS, Gardner D., 1st Lieut., Chicago, Station Hospital, Camp Grant, Ill.
RAND, George I., Captain, Chicago, Station Hospital, Camp Grant, Ill.
RUBENSTEIN, Hyman I., Captain, Chicago, Fort Sheridan, Ill.
REDMOND, Ralph N., 1st Lieut., Sterling, Ill., Station Hospital, Camp Grant, Ill.
SAZAMA, Francis J., 1st Lieut., Berwyn, Ill., Fort Custer, Mich.
SCHOWENGERDT, William H., Captain, Champaign, Ill., Gamp Grant, Ill.
SEXTON, George A., 1st Lieut., Monticello, Ill., Station Hospital, Camp Grant, Ill.
STEIN, Morris F., Captain, Chicago, Station Hospital, Camp Grant, Ill.
ST. PIERRE, Roderick G., Captain, Portland, Ore., Fort Sheridan, Ill.
THRIFT, Chester B., Captain, Chicago, Fort Sheridan, Ill.
WEICHSELBAUM, Paul K., 1st Lieut., Chicago, Station Hospital, Camp Grant, Ill.
YOUNG, Joseph J., 1st Lieut., Appleton, Wis., Station Hospital, Camp Grant, Ill.

## SEVENTH CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding Officer, Seventh Corps Area, up to January 10. The Seventh Corps Area comprises the states of North Dakota, South Dakota, Minnesota, Nebraska, Iowa, Kansas, Missouri, Arkansas and Wyoming.

ADLER, Morton William, 1st Lieut., Vandalia, Mo., Fort Snelling, Minn.
ALDERSON, Donald Marr, 1st Lieut., Gering, Neb., Camp Murray, Wash.
BENJAMIN, Edwin Grimshaw, 1st Lieut., Minneapolis, Fort Sam Houston, Texas.
BETTLER, Philip Leon, 1st Lieut., Sioux City, Iowa, Rolla, Mo.
BINNS, Van Carl, Captain, Monticello, Ark., Fort Bliss, Texas.
BOHRER, Edward Royse, 1st Lieut., West Plains, Mo., Fort Riley, Kan.
BOZARTH, Elton Poole, 1st Lieut., Humboldt, Neb., Rolla, Mo.
BRYAN, Emery Clarence, 1st Lieut., Erie, Kan., Jefferson Barracks, Mo.
CONNOR, Samuel Walters, Major, Camdenton, Mo., Fort Bliss, Texas.
DOSS, William Norman, 1st Lieut., Leon, Iowa, Camp Murray, Wash.
DUSHKIN, Milton Arnold, Captain, Des Moines, Iowa, Fort Clark, Texas.
DWORKIN, Shiell, 1st Lieut., St. Louis, Camp Joseph T. Robinson, Ark.
ELSON, Veryl J., 1st Lieut., Danbury, Iowa, Fort Sam Houston, Texas.
EVANS, Ezra Levi, Jr., Captain, Springfield, Mo., Fort Riley, Kan.
GLASSCOCK, James Richard, Captain, St. Louis, Fort Snelling, Minn.
HAYMOND, Harold Everest, Captain, Perry, Iowa, Fort Meade, S. D.
HENDERSON, Lauren James, 1st Lieut., Cedar Falls, Iowa, Fort Ord, Calif.
HIRSCHFELD, Beryl, 1st Lieut., North Platte, Neb., Fort Snelling, Minn.
JOHNSON, Harold Clark, 1st Lieut., Thief River Falls, Minn., Fort Sam Houston, Texas.
JOHNSON, Julius Doar, Captain, Fort Smith, Ark., Fort Snelling, Minn.
KELLEY, Gilbert Byron, 1st Lieut., Savannah, Mo., Fort Sam Houston, Texas.
KETTLEWELL, Ralph Burnsell, Captain, Sauk Center, Minn., Fort Riley, Kan.
LARSEN, Kenneth Victor, Captain, St. Louis, Fort Clark, Texas.
LEVIN, Abraham Jacob, 1st Lieut., St. Louis, Fort Lewis, Wash.
MILLER, Richard White, 1st Lieut., Fayetteville, Ark., Jefferson Barracks, Mo.
RICHARDSON, Frank Lloyd, 1st Lieut., Minneapolis, Carlisle Barracks, Pa.
SNIPES, James Johnson, Major, Lincoln, Neb., Fort Snelling, Minn.
SWARTWOOD, Francis Marion, Major, Adams, Neb., Fort Lewis, Wash.
WILCOX, Keith Eugene, 1st Lieut., Sioux City, Iowa, Carlisle Barracks, Pa.

### CORRECTION

In THE JOURNAL, January 11, page 147, in the Seventh Corps Area list of medical reserve officers ordered to active duty, the name Morton appears as the last name, whereas it is the first name of Morton William Adler.

## EIGHTH CORPS AREA

The following additional medical reserve corps officers had been ordered to active duty by the Commanding General, Eighth Corps Area, up to January 10. The Eighth Corps Area comprises the states of Colorado, Arizona, New Mexico, Oklahoma and Texas.

BADEN, Ervin Edgar, 1st Lieut., Raymondville, Texas, 45th Division, Fort Sill, Okla.
BAMBERGER, Paul J., 1st Lieut., Climax, Colo., 45th Division, Fort Sill, Okla.
BLOOM, Bernard H., 1st Lieut., San Antonio, Texas., 45th Division, Fort Sill, Okla.
CARRICO, Carl C., 1st Lieut., Houston, Texas, 45th Division, Fort Sill, Okla.
CHASE, Gaylord R., 1st Lieut., Longmont, Colo., 45th Division, Fort Sill, Okla.
De VORE, Neal M., Captain, Houston, Texas, 45th Division, Fort Sill, Okla.
FOX, Fred T., 1st Lieut., Lawton, Okla., 45th Division, Fort Sill, Okla.
HATFIELD, Haskell D., Captain, Baytown, Texas, 45th Division, Fort Sill, Okla.
LEDBETTER, William Harry, 1st Lieut., Wichita Falls, Texas, Fort Sam Houston, Texas.
McKELLAR, Thomas F., 1st Lieut., Pflugerville, Texas., 45th Division, Fort Sill, Okla.
MOSER, Emil Roland, 1st Lieut., Gladewater, Texas, 45th Division, Fort Sill, Okla.
OCHS, Jacob, 1st Lieut., Columbus, N. M., 2d Quartermaster Battalion, Fort Sam Houston, Texas.
SCIRE, Feliciano J., 1st Lieut., Keams Canyon, Ariz., 2d Medical Battalion, Fort Sam Houston, Texas.
SEWELL, Dan R., Captain, Oklahoma City, Selective Service Board, Oklahoma City.
SHERMAN, Leon H., 1st Lieut., Denver, Fort Sam Houston, Texas.

### Orders Revoked

Orders of the following officers previously reported have been revoked:

BEST, Ralph L., 1st Lieut., Skiatook, Okla.
DAILY, Robert L., 1st Lieut., Wichita Falls, Texas.
ETTER, Edward F., Captain, Sherman, Texas.
GALT, Sidney, Captain, Dallas, Texas.
LAMB, Marvin, 1st Lieut., Jacksonville, Texas.
MAXFIELD, James Robert, Captain, Albuquerque, N. M.
MONTGOMERY, Eugene Porter, 1st Lieut., Boston.
PERRY, Herbert Allen, 1st Lieut., Medical Lake, Wash.
ROBINETT, James Bradley, Jr., 1st Lieut., Houston, Texas.

## NINTH CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty up to January 11 by the Commanding General, Ninth Corps Area (Washington, Montana, Oregon, Nevada, Utah, California and Idaho).

AUERBACH, Oscar, 1st Lieut., Los Angeles, 19th Engineers, Fort Ord, Calif.
CAMPBELL, Myron M., 1st Lieut., Seattle, 41st Division, Camp Murray, Wash.
CANE, Edward M., 1st Lieut., Los Angeles, Fort Lewis, Wash. (first to Carlisle Barracks for "refresher" course).
FISHMAN, Harold C., 1st Lieut., Los Angeles, Fort Ord, Calif.
GOLDSTEIN, David M., 1st Lieut., Los Angeles, Camp San Luis Obispo, Calif.
HAMILTON, Robert S., 1st Lieut., Los Angeles, Camp San Luis Obispo, Calif.
PARROTT, Robert M., 1st Lieut., assigned to Fort Lewis, Dec. 14, 1940, relieved from active duty, Dec. 31, 1940.
TAYLOR, Edward D., Captain, Centralia, Wash., Fort Lewis, Wash. (erroneously reported as 1st Lieutenant).

# WAR DEPARTMENT ORDERS

ALLING, Emery E., Major, from the Presidio of San Francisco to the Panama Canal Department.
BENNETT, Eaton W., Captain, from the Hawaiian Department to Army Medical Center, Washington, D. C.
BILLICK, Eugene W., Major, from Philippine Department to Fort Ord, Calif.
COOK, Everett L., Lieut. Col., from Hawaiian Department to the Office of the Surgeon General, Washington, D. C.
COOK, Walter R., Captain, from Fort Fort Benjamin Harrison, Ind., to the Hawaiian Department.
CRAIG, Joseph S., Lieut. Col., from Fort Lawton, Wash., to the Philippine Department.
CRAIG, William R., Major, from Fort Douglas, Utah, to the Philippine Department.
CULLEN, John K., Captain, from the Hawaiian Department to San Francisco Port of Embarkation, Fort Mason, Calif.
GRANADE, John E., Captain, from the Philippine Department to the New York Port of Embarkation, Brooklyn.
GREEN, Mack M., Major, from the Panama Canal Department to the New York Port of Embarkation.
LANE, Frank H., Captain, East St. Louis, Ill., to the Hawaiian Department.
LEWIS, Robert B., Captain, from Washington, D. C., to the Philippine Department.
MOORE, Prentice L., Major, from the Hawaiian Department to Carlisle Barracks, Pa.
O'DONNELL, John W., Captain, from the Hawaiian Department to the San Francisco Port of Embarkation, Fort Mason, Calif.
ROBERTS, John E., Captain, from the Hawaiian Department to Moffett Field, Calif.
SMITH, Andrew W., Lieut. Col., from McShord Field, Wash., to Hawaiian Department, sailing from San Francisco January 23.
SMITH, Philip J., Captain, from Fort Dupont, Del., to the Hawaiian Department.
TODD, William A., Jr., Captain, from the Philippine Department to the New York Port of Embarkation, Brooklyn.
WARD, Donald M., Captain, from the Philippine Department to the New York Port of Embarkation, Brooklyn.
WASKOWICZ, Aloysius T., Captain, from the Hawaiian Department to the New York Port of Embarkation.
WESTERVELT, Frederic B., Captain, from Hawaiian Department to Fort Mason, Calif.
YOUNG, Charles T., Major, from Fort Sam Houston, Texas, to Hawaiian Department, sailing from San Francisco March 1.

# ORGANIZATION SECTION

## OFFICIAL NOTES

### RADIO BROADCASTS

"Doctors at Work" is the title of the sixth annual series of dramatized radio programs being presented by the American Medical Association and the National Broadcasting Company.

The series opened Wednesday, November 13, and will run for thirty consecutive weeks, closing with a broadcast from the A. M. A. meeting at Cleveland on June 4. The program is scheduled for 10:30 p. m. eastern standard time (9:30 central, 8:30 mountain, 7:30 Pacific time) over the Blue network, other N. B. C. stations and Canadian stations.

Some radio stations may be unable to broadcast the program at the regular scheduled time and may transcribe and broadcast it at another hour or even on another day. It is advisable therefore to verify the time by reference to local newspapers or by telephoning the local Blue network stations.

The programs will dramatize what modern medicine offers the individual in the way of opportunities for better health and the more successful treatment of disease. Incidental to this main theme the programs will explain the characteristics of the different fields of modern medicine and its specialties.

Descriptive posters for local distribution may be had gratis from the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Program titles will be announced weekly in THE JOURNAL and monthly in *Hygeia,* the Health Magazine.

Tickets are available for each broadcast. Address the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Tickets are free, but a stamped self-addressed envelop should accompany requests.

The next three programs to be broadcast, together with their dates and titles, are as follows:

January 29. Deeper Than It Looks.
February 5. New Faces for Old.
February 12. Medical Detective.

### ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE

#### Program of Meetings to be Held in Chicago February 17 and 18

The Thirty-Seventh Annual Congress of the Council on Medical Education and Hospitals of the American Medical Association will be held at the Palmer House, Chicago, February 17 and 18. The Federation of State Medical Boards of the United States will participate in the congress. The program follows:

MONDAY, FEBRUARY 17, 10 A. M.
*RAY LYMAN WILBUR, M.D., Presiding*

*Some War Aspects of Medicine.*
Ray Lyman Wilbur, M.D., Chairman, Council on Medical Education and Hospitals, Stanford University, Calif.
*The Contribution of Liberal Education to Professional Studies.*
Oliver C. Carmichael, LL.D., Chancellor, Vanderbilt University, Nashville, Tenn.
*Universities and the People's Health.*
Raymond B. Allen, M.D., Executive Dean, Chicago Colleges, University of Illinois.
*The Challenge to Hospitals in the Changing Attitude Toward Them.*
Rt. Rev. Maurice F. Griffin, LL.D., Trustee, American Hospital Association, Cleveland.
*Adjustment of Medical Education to Social Demand.*
Chauncey D. Leake, Ph.D., Professor of Pharmacology, University of California Medical School, San Francisco.

*RED LACQUER ROOM*

MONDAY, FEBRUARY 17, 2 P. M.
*RAY LYMAN WILBUR, M.D., Presiding*

*The Physician in Selective Service.*
Col. Leonard S. Rowntree, Chief of the Medical Division, Selective Service System, Washington, D. C.
*Educational Purposes of the Standard Nomenclature of Disease.*
Edwin P. Jordan, M.D., Assistant Editor, *The Journal* of the American Medical Association, Chicago.
*The Objective of Medical Education.*
Samuel C. Harvey, M.D., William H. Carmalt Professor of Surgery, Yale University School of Medicine, New Haven.
*A School of Dental Medicine.*
C. Sidney Burwell, M.D., Dean, Harvard Medical School, Boston.
*The Problem of the Premedical Student in a Physics Department.*
Harvey B. Lemon, Ph.D., Professor of Physics, University of Chicago.
*Undergraduate and Graduate Medical Education for Negroes.*
Edward L. Turner, M.D., Meharry Medical College, Nashville, Tenn.

*RED LACQUER ROOM*

TUESDAY, FEBRUARY 18, 9:30 A. M.

JOINT SESSION OF THE COUNCIL ON MEDICAL EDUCATION AND HOSPITALS AND THE FEDERATION OF STATE MEDICAL BOARDS

*JOHN R. NEAL, M.D., Presiding*

*The Function of the Museum in the Medical School.*
William Boyd, M.D., Professor of Pathology and Bacteriology and Curator of the Museum and Laboratories, University of Toronto Faculty of Medicine.
*Purpose, Content and Methods of Teaching Public Health to Medical Students.*
Haven Emerson, M.D., Emeritus Professor of Public Health Practice, Columbia University College of Physicians and Surgeons, New York.
*The Confused State of the Hospital Internship.*
Reginald Fitz, M.D., Member, Council on Medical Education and Hospitals, American Medical Association, Boston.
Discussion: Malcolm T. MacEachern, M.D., Chicago.
*A Naturopathic Subterfuge: Purported Licensure by State Naturopathic Associations.*
J. W. Holloway Jr., Acting Director, Bureau of Legal Medicine and Legislation, American Medical Association, Chicago.
Discussion: G. M. Williamson, M.D., Grand Forks, N. D.
*The National Board of Medical Examiners as Related to Medical Licensure.*
Everett S. Elwood, Executive Secretary and Treasurer, National Board of Medical Examiners, Philadelphia.
Discussion: Roy B. Harrison, M.D., New Orleans.
*Basic Science Boards and Medical Licensure.*
Charles Carter, Ph.D., Chairman, Iowa Board of Examiners in the Basic Sciences, Fairfield, Iowa.
Discussion: Thomas P. Murdock, M.D., Meriden, Conn.

*RED LACQUER ROOM*

THE FEDERATION OF STATE MEDICAL BOARDS

MONDAY, FEBRUARY 17
FEDERATION DINNER
6:30 P. M.

*Medicine in National Emergencies.*
Ray Lyman Wilbur, M.D., President, Stanford University, Stanford University, Calif.
*Presidential Address.*
John R. Neal, M.D., President, Federation of State Medical Boards of the United States, Chicago.
*Round Table Discussion.*

TUESDAY, FEBRUARY 18
FEDERATION LUNCHEON
12:30 P. M.

TUESDAY, FEBRUARY 18, 2 P. M.
*JOHN R. NEAL, M.D., Presiding*

*What Is Wrong with the Teaching of Materia Medica and Therapeutics in Medical Schools?*
Adam P. Leighton, M.D., Secretary, Maine Board of Registration of Medicine, Portland.
*Control of Practice Violators.*
Julian F. Du Bois, M.D., Secretary; F. Manley Brist, Attorney, Minnesota Board of Medical Examiners, St. Paul.
*The Physician's Responsibility in Law Enforcement.*
I. D. Metzger, M.D., Chairman, Pennsylvania State Board of Medical Education and Licensure, Pittsburgh.
*Residence Requirement and Interstate Endorsement.*
J. W. Bowers, M.D., Secretary, Indiana State Board of Medical Registration and Examination, Fort Wayne.
*Executive Session.*

*RED LACQUER ROOM*

CENTRAL COUNCIL FOR NURSING EDUCATION
MONDAY, FEBRUARY 17, 12:15 P. M.

Luncheon for Lay Boards of Hospitals and Public Health Nursing Organizations.
*The Meaning of Home Defense*
Miss Mary Beard, R.N., National Director, American Red Cross Nursing Service, Washington, D. C.

*GRAND BALL ROOM*

# MEDICAL LEGISLATION

## MEDICAL BILLS IN CONGRESS

*Bills Introduced.*—S. 27, introduced by Senator Caraway, Arkansas, proposes to authorize the refund of certain amounts collected from physicians between June 1, 1920 and June 30, 1931 for the privilege of prescribing the waters from Hot Springs National Park. S. 146, introduced by Senator White, Maine, proposes to grant pensions to male nurses who served under contract between April 21, 1898 and February 2, 1901. S. 286, introduced by Senator Sheppard, Texas, provides that the retired personnel of the Army, Navy, Marine Corps, and Coast Guard, and Fleet Naval and Fleet Marine Corps reservists requiring hospitalization shall be entitled to enter any Army or Navy hospital on their own personal request, under the same conditions as are now, or which hereafter may be fixed for the active service. H. R. 20, introduced by Representative Bland, Virginia, proposes to extend the benefits of the United States Employees' Compensation Act to employees of the Federal Civil Works Administration. H. R. 62, introduced by Representative Cannon, Missouri, proposes that all public laws granting medical and hospital treatment, domiciliary care, compensation and other allowances, pensions, disability allowance and retirement pay to veterans and dependents of veterans of the World War which were repealed in 1933 be reenacted. H. R. 84, introduced by Delegate Dimond, Alaska, contemplates the extension of the benefits of the United States Public Health Service to any person operating or employed on board certain vessels engaged in fishing operations. H. R. 98, introduced by Representative Dondero, Michigan, proposes to regulate the interstate transportation of containers of milk and other dairy products. H. R. 101, introduced by Representative Hull, and H. R. 1389, introduced by Representative Gehrmann, both of Wisconsin, propose to enact a "Dairy Products Stabilization Act" so as to provide for the promotion of sound dairy practices and to provide an adequate and balanced flow of milk and its products in interstate and foreign commerce. H. R. 124, introduced by Representative Culkin, New York, proposes, among other things, that no person shall manufacture, import into the United States, transport in interstate or offer, sell or have in his possession for sale any oleomargarine, margarine, butterine or other substitutes for butter, manufactured wholly or in part from any fat other than that of milk or cream. H. R. 149, introduced by Representative Tenerowicz, Michigan, proposes a federal appropriation of $250,000 to provide an addition to the Veterans' Administration hospital at Dearborn, Mich., to accommodate 250 patients. H. R. 156, introduced by Representative Voorhis, California, provides for the issuance by the Administrator of Veterans' Affairs of regulations providing for more liberal policies in determining the service connection of disabilities. H. R. 168, introduced by Representative Welch, California, provides for the construction of a marine tuberculosis hospital in California. H. R. 633, introduced by Representative Rogers, Massachusetts, provides that notwithstanding any provision of law or veterans' regulations, any World War ex-service man shown to have active tuberculosis of compensable degree shall be deemed to be totally disabled for purposes of compensation when hospitalized. H. R. 951, introduced by Representative Angell, Oregon, proposes a federal appropriation not to exceed $2,500,000 to construct at Portland, Ore., a hospital for the care and treatment of the insane of the Territory of Alaska and of such other classes of persons who are insane or who may require mental treatment as the President may designate for care and treatment in the hospital. H. R. 958, introduced by Representative Angell, Oregon, and H. R. 1825, introduced by Representative Boland, Pennsylvania, propose an annual federal appropriation of $11,580,000 to assist the states in the education of all children who are crippled, blind, partially seeing, deaf, hard of hearing, defective in speech, cardiopathic, tuberculous or otherwise physically handicapped and who for their education require an expenditure of money in excess of the cost of educating physically normal children. The administration of this bill will devolve on the Commissioner of Education. H. R. 960, introduced by Representative Angell, Oregon, proposes to extend the benefits of the Social Security Act to include individuals who are physically disabled. H. R. 961, introduced by Representative Angell, Oregon, proposes to pay an annuity at a rate not to exceed $50 per month to blind persons whose annual income is less than $1,200, the term "blind person" being defined to mean a person who is 21 years of age or over and a citizen of the United States with not more than 20/20 of visual acuity in the better eye with maximum correction or whose field of vision is limited to 20 degrees or less from the fixation point in all quadrants. H. R. 995, introduced by Representative Patrick, Alabama, proposes to add a new title to the Social Security Act under which financial aid will be given to the states for the relief of the blind. The bill contemplates the furnishing of hospitalization, medical and surgical aid to needy blind individuals. H. R. 1008, introduced by Representative Rogers, Massachusetts, will, if enacted, provide prosthetic appliances to certain veterans suffering from non-service connected disabilities. H. R. 1022, introduced by Representative Geyer, California, proposes a federal appropriation not to exceed $2,500,000 for the construction of a marine hospital at Los Angeles Harbor, Los Angeles. H. R. 1025, introduced by Representative Jenkins, Ohio, would authorize the payment of claims for unauthorized emergency treatment of disabled veterans in case no veterans' administration facilities are available. H. R. 1033, introduced by Representative Ludlow, Indiana, directs the Secretary of the Treasury to cause to be struck a medal of appropriate design with suitable emblems, devices and inscriptions, or a certificate suitable for framing, to commemorate the faithful nursing by the women who voluntarily offered their services and who served with the Army during the influenza epidemic of 1918. H. R. 1038, introduced by Representative Peterson, Georgia, provides for pensions to peacetime veterans of the regular Army, Navy, Marine Corps and Coast Guard suffering from arrested tuberculosis contracted while in the service. H. R. 1110, introduced by Representative Spence, Kentucky, proposes to create a Division of Water Pollution Control in the United States Public Health Service and to authorize the Division to prepare comprehensive plans for eliminating or reducing the pollution and improving the sanitary condition of the navigable waters of the United States and streams tributary thereto. The bill further proposes annual federal appropriations not to exceed $50,000,000 to be available for grants-in-aid or loans to any state, municipality or other public body for the construction of necessary treatment works. H. R. 1391, introduced by Representative Gehrmann, Wisconsin, proposes to prohibit the importation of dairy products into the United States unless such products have been produced from milk or cream of cows which are either free from bovine tuberculosis and Bang's disease or which are under test for bovine tuberculosis and Bang's disease. H. R. 1395, introduced by Representative Green, and H. R. 2092, introduced by Representative Peterson, both of Florida, provide for the construction of a marine hospital in Florida. H. R. 1397, introduced by Representative Green, Florida, proposes a federal appropriation of $2,500,000 for the construction of a marine hospital at Jacksonville, Fla. H. R. 1421, introduced by Representative Pace, Georgia, proposes a federal appropriation of $2,500,000 for the construction of a veterans' hospital for the southwest section of Georgia, with a capacity of at least 800 beds. H. R. 1587, introduced by Representative Celler, New York, proposes, among other things, that wherever a veteran seeking service connection is shown to have been engaged in combat with the enemy, or to have been subjected to other conditions within the zone of advance, which can, in good medical judgment, be considered as causing or aggravating the disability or disabilities on which the claim is based, then the disability or disabilities shall be considered to have been caused or aggravated by military service. H. R. 1633, introduced by Representative Sheppard, California, proposes a federal appropriation of $500,000 to construct a 200 bed veterans' hospital primarily for treatment of diseases of the chest, the hospital to be located in the Mojave Desert of either San Bernardino or Riverside County, Calif. H. R.

1798, introduced by Representative Sutphin, New Jersey, contemplates a complete survey of the physical education resources existing within the United States, such as outdoor recreative and competitive areas, gymnasiums, stadiums, swimming pools, and parks for the purpose of formulating a program to enable the youth of the nation to participate in supervised physical activities. H. R. 2082, introduced by Representative Flannery, and H. R. 2090, introduced by Representative Moser, both of Pennsylvania, propose to authorize the Secretary of the Interior to make certain inspections in coal mines to obtain information relative to health and safety conditions and occupational diseases. H. R. 2102, introduced by Representative Van Zandt, Pennsylvania, provides that in the administration of laws, regulations or rules by the United States Civil Service Commission there shall be no bar to the consideration of applications for employment under the federal government by World War veteran physicians or dentists by reason of time elapsing between graduation from medical schools of recognized standing and the date of application for examination or employment as physician or dentist. H. R. 2103, introduced by Representative Van Zandt, Pennsylvania, provides that any person who served in the military or naval forces of the United States during a recognized campaign or expedition, and who was honorably separated from such service, shall be granted hospitalization and domiciliary care by the Veterans' Administration subject to the same restrictions and limitations as are now applicable to World War veterans. H. R. 2105, introduced by Representative Van Zandt, Pennsylvania, would require the Administrator of Veterans' Affairs to amend the rating schedules so as to provide total ratings for the most severe functional nervous diseases or psychoneurotic states. H. R. 2108, introduced by Representative Vinson, Georgia, proposes to authorize the Secretary of the Navy to establish naval hospitals at the Naval Air Stations at Jacksonville, Fla., Corpus Christi, Texas, and San Juan, P. R.; the submarine base, Coco Solo, C. Z.; the naval station, Guantanamo Bay, Cuba, and the Marine barracks, Quantico, Va. H. R. 2112, introduced by Representative Vinson, Georgia, proposes to authorize the Secretary of the Navy to appoint in time of war or national emergency declared by the President to exist, for temporary service, such acting assistant surgeons as the exigencies of the service may require, who shall receive the compensation of assistant surgeons. S. J. Res. 10, introduced by Senator Sheppard, Texas, provides that enlisted men of the Army, Navy, Marine Corps and Coast Guard, when hospitalized or domiciled in either an army or navy hospital or the United States Soldiers' Home, shall be extended such treatment or domiciliary care without cost. S. 164, introduced by Senator Sheppard, Texas, and H. R. 2278, introduced by Representative May, Kentucky, propose to authorize the Secretary of War to detail not to exceed 2 per cent of the enlisted men of the regular army as students at such technical, professional and other educational institutions or as students, observers or investigators at such industrial plants, hospitals and other places as shall be best suited to enable such enlisted men to acquire a knowledge of or experience in the specialties in which it is deemed necessary that such enlisted men shall perfect themselves. S. 197, introduced by Senator Murray, Montana, proposes to amend the Selective Training and Service Act of 1940 so as to provide that any man selected for training and service under the act who has been awarded a degree of doctor of medicine or doctor of dental surgery by recognized medical or dental schools, who holds a valid license to practice medicine, surgery or dentistry in any state, territory or possession of the United States or the District of Columbia, and who is engaged in such practice at the time of his selection, and whose physical and mental fitness for such training and service has been satisfactorily determined shall, in lieu of induction for such training and service, be commissioned as an officer in the Medical Department Reserve, Officers' Reserve Corps, and ordered into active military service as provided by law. This bill further provides that medical and dental students at recognized medical and dental schools and interns and resident physicians, surgeons and dentists at recognized hospitals shall be exempt from training and service, but not from registration, under the act. Any such medical or dental student, intern or resident physician, surgeon or dentist, the bill further provides, who is a member of a reserve component of the land or naval forces of the United States shall not be ordered or called to active duty or into active service in any of such forces without his consent, except in time of war. H. R. 549, introduced by Representative Merritt, New York, proposes a federal appropriation of $1,875,000 to construct, at Whitehall, N. Y., or vicinity, a modern fireproof general medical-surgical veterans hospital and domiciliary facility, with a capacity of at least six hundred beds. H. R. 1007, introduced by Representative Rogers, Massachusetts, proposes a federal appropriation of $2,300,000 for the first year of operation of the bill, and thereafter such sums as may be necessary, to enable the Public Health Service to assist states, counties, cities or other political subdivisions of the states to extend and improve measures through public and private institutions and organizations for the diagnosis, treatment and control of cancer, including the provision of hospital, diagnostic, clinic and other facilities for the diagnosis and treatment of persons suffering from cancer or suspected of suffering from this disease. H. R. 1074, introduced by Representative Schwert, New York, proposes to promote national preparedness and the national welfare through appropriation of funds to assist the several states and territories in making adequate provisions through schools for physical education, including athletics, instruction and guidance in healthful living, wider recreational use of school facilities and the development of school camps. H. R. 1425, introduced by Representative Peterson, Florida, proposes to authorize the Administrator of Veterans' Affairs to furnish outpatient treatment or medication, including pneumothorax therapy, insulin and liver extract, to honorably discharged veterans of the World War requiring such treatment or medication, notwithstanding that the disease necessitating the treatment or medication may not be directly or presumptively service connected. H. R. 1791, introduced by Representative Pfeifer, New York, proposes to establish a federal Department of Health. This department, it is proposed, will, among other activities, conduct researches, experiments and surveys, formulate and foster plans and compile and disseminate information for the purpose of promoting and maintaining health and sanitation. At the head of this department, it is proposed, will be a Secretary of Health, who must be a member of the medical profession. If the bill should be enacted, there will be transferred to the new department the Food and Drug Administration, the Division of Vital Statistics of the Bureau of the Census, Freedmen's Hospital and Saint Elizabeths Hospital, the Children's Bureau, and all functions of the United States Public Health Service, of the Bureau of Narcotics, and the Health Department of the District of Columbia.

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## STATE MEDICAL LEGISLATION

### California

*Bills Introduced.*—S. 61, to amend the law relating to private institutions for insane and incompetent persons, proposes to impose an annual license fee on such institutions, the amount of which is to vary in accordance with the number of patients a particular institution is licensed to care for. For institutions licensed to receive not more than 20 patients, the fee proposed is $5; for those licensed to receive more than 20 patients but not more than 25, the fee proposed is $25; and for institutions licensed to receive more than 25 patients, the fee proposed is $50. Under the present law the annual license fee is $50 regardless of the number of patients for whom the institution is licensed to care. S. 130, to amend the use tax act, proposes to exempt from its provisions the storage, use or other consumption in the state of medicines and drugs used in the diagnosis, cure, mitigation, treatment or prevention of disease in man. Medicines and drugs, as so defined, are not to include any instrument or apparatus. A. 51 proposes to enact a new massage practice act and to vest the administration of that act in a state board of massage, to be appointed by the governor and to consist of three members who must have been actively engaged in the practice of massage for not less than three years preceding the date of their appointment. The bill proposes to define the practice of massage as "the use or employment of any method, art or science of administering to the human body for hygienic or therapeutic purposes exclusively, by rubbing, stroking, kneading, tapping or rolling the same manually, or the

external application or water, either natural or mineral to the human body, for the purpose of relieving or alleviating affected parts thereof." The bill proposes to exempt from its provisions persons duly licensed in the state to practice medicine, surgery, osteopathy, "drugless physician," [sic] chiropody or chiropractic and registered nurses while acting under the direct supervision of a "medical doctor." Certain present practitioners of massage, now residing in the state, are to be licensed without examination. Other applicants who are licensed to practice massage must furnish a satisfactory "testimonial" of good moral character and must furnish satisfactory evidence of graduation from a school or institution approved by the board. Apparently the board can approve only such an institution as requires a course of instruction of not less than thirty-four weeks, and a total number of hours for all courses of not less than one thousand hours as a condition precedent to graduation. A. 2, to amend the unemployment insurance act, proposes in effect to make unemployment insurance available to an employee who is unemployed because of illness and on whose behalf there is presented a certificate, signed by a licensed physician and surgeon, that the employee was unable to work during the period for which benefits were claimed because of illness.

### Maryland

*Bills Introduced.*—H. 76 proposes that whenever the defendant in bastardy proceedings denies that he is the father of the child, and so petitions, the court shall order the complaint, the child and the defendant to submit to such blood tests as may be deemed necessary to determine whether or not the defendant can be excluded as being the father of the child. The result of the test is to be admissible in evidence only in cases in which definite exclusion is established. H. 34 proposes to authorize the Department of Public Welfare to establish two institutions for needy persons who require medical, nursing or custodial care by reason of chronic illness or infirmity.

### Massachusetts

*Bills Introduced.*—H. 341 proposes that any town not maintaining or managing a hospital may annually appropriate not exceeding $1,000 to a hospital established in such town or its vicinity for the establishment and maintenance of a free bed in the hospital for the care and treatment of persons who are residents of the town and unable to pay for necessary medical care and treatment. H. 215 proposes to require the operator of a motor vehicle involved in an accident, collision or violation of the automobile laws to report to the registrar of motor vehicles for a medical examination, the standards of which are to be made public from time to time. H. 272 proposes to appropriate $25,000 to the board of registration in medicine to investigate and prosecute violations of the medical practice act and of the rules and regulations promulgated thereunder by the board.

### Michigan

*Bills Introduced.*—S. 50 proposes to appropriate $435,452.13 as a supplementary appropriation for the Michigan crippled children commission for the fiscal year ending June 30, 1941. S. 21 proposes to supplement former appropriations to the Michigan crippled children commission for the fiscal year ending June 30, 1941 in the following manner for the purposes stated: medical treatment of crippled children $150,000; medical treatment of afflicted children $300,000; unpaid bills and balance on prorated bills, medical treatment of crippled children $78,788.61, and medical treatment of afflicted children $356,663.52.

### New York

*Bill Introduced.*—A. 167 proposes to permit physicians and nurses to disclose professional information acquired in attending a patient in a professional capacity where it appears that the patient has been the victim of professional negligence or incompetence which is the subject of a legislative investigation by the state or a political subdivision thereof.

### Oklahoma

*Bills Introduced.*—S. 13 proposes that the committee on standardization of hospitals for crippled children shall consist of six members, one of whom must be a licensed dentist. H. 44 proposes to require food handlers to submit to physical examinations, including blood tests semiannually and to possess a certificate signed by the appropriate county health officer, showing they are free from syphilis, gonorrhea and tuberculosis.

### Tennessee

*Bills Introduced.*—H. 102 authorizes the sexual sterilization of inmates of state institutions who are habitual criminals or are afflicted with hereditary forms of insanity that are recurrent, idiocy, imbecility, feeblemindedness or epilepsy. H. 172 and S. 120, to amend the chiropractic practice act, proposes (1) to define chiropractic as the science of "palpating, analyzing and adjusting the articulations of the human spinal column and adjacent tissues by hand," (2) to condition the annual removal of a license on presentation of proof that the licentiate has attended at least one of the semiannual sessions of the Tennessee Chiropractic Association during the year next preceding such application for renewal of license, and (3) to make eligible for examination for a license to practice any person who is a graduate of a school or college of chiropractic giving adequate courses in anatomy, physiology, bacteriology, pathology, chemistry, symptomatology, spinal analysis, hygiene, sanitation, principles and practice of chiropractic, and chiropractic philosophy, which school as a condition precedent to graduation required actual attendance of four school years of not less than nine months each.

## WOMAN'S AUXILIARY

### Kentucky

The third midyear board meeting of the Woman's Auxiliary to the Kentucky State Medical Association was held at Louisville, November 12, with the president, Mrs. John M. Blades, Butler, presiding. Honored guests were the President of the Woman's Auxiliary to the American Medical Association, the president and president-elect of the Woman's Auxiliary to the Southern Medical Association and the president of the Kentucky State Medical Association. Dr. Austin Bell, Hopkinsville, president of the state association, outlined some objectives which the auxiliary might undertake.

### Wisconsin

Mrs. Donne F. Gosin of Green Bay, president of the state auxiliary, spoke at the November meeting of the Fond du Lac County auxiliary, her subject being the "Aims of Our Organization." Mrs. Ernest S. Schmidt, state chairman of organization, also spoke. A talk on girl scouts was given by Mrs. Claude Musolf of Fond du Lac. The Fond du Lac auxiliary sponsors a girl scout troop, donates money to the Children's Home and makes bandages for the Red Cross.

The Rock County auxiliary held its annnal meeting, October 30, at Janesville with Mrs. H. E. Kasten of Beloit presiding. Annual reports of the Hygeia and philanthropic committees revealed that this group of thirty-five women had placed copies of *Hygeia* in homes, schools and libraries; had worked for the benefit of Mercy Hospital in Janesville and of Beloit Municipal Hospital, and had provided Christmas gifts and entertainment for all the patients at Pinehurst Sanitarium.

The Sauk County auxiliary, organized this year, met October 10 at Sauk City with Mrs. C. D. Pope presiding. The new project of this group is the making of layettes for use as needed by the doctors of the county.

The Sheboygan County auxiliary held its annual meeting, October 2, at Rocky Knoll Sanitarium, Plymouth. Mrs. A. J. Brickbauer is the new president.

# Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

ADDITIONAL MEDICAL COLLEGE NEWS AND ARTICLES APPEAR IN THE STUDENT SECTION, PAGE 339.

## ALABAMA

**Changes in Health Officers.**—Dr. Rutherford O. Ingham, Livingston, formerly health officer of Bibb County, has been assigned to a similar position in Limestone County. Dr. Robert W. Todd, New Orleans, has been appointed health officer of Russell County, succeeding Dr. Marion L. Shaddix, Phenix City, who recently was transferred to Clay County. Dr. Ralph H. Allen, formerly of Ruston, La., has been placed in charge of the health activities in Henry County. Dr. Bertha E. Stokes, Union Springs, has been appointed health officer of Bullock County, succeeding Dr. Delmer F. Parker, who resigned to enter the Indian Service of the U. S. Department of Interior, it is reported. Dr. Stokes will have her headquarters in Union Springs.

## CALIFORNIA

**Society News.**—The San Francisco County Medical Society was addressed January 14 by Dr. Walter C. Alvarez, Rochester, Minn., on "Abdominal Pain." A report on illness and hazards in automobile driving was submitted and discussed by Fred P. Williams, supervisor, California State Department of Motor Vehicles, division of drivers' licenses.

**New Cardiovascular Research Laboratory.**—A cardiovascular research laboratory will be opened at Mount Zion Hospital, San Francisco, January 31, under the direction of Dr. Meyer Friedman. A two day celebration will mark the opening, at which Dr. Louis N. Katz, Chicago, will present papers entitled "Role of Normal Kidney in Renal Hypertension" and "The Electrocardiogram in Coronary Disease," and Dr. Emanuel Libman, New York, "Pain" and "Libman-Sacks Disease."

**Health Defense Week.**—The week of February 2 to 9 has been designated "Health Defense Week" in Los Angeles. A resolution asking for a proclamation was presented to the mayor by a delegation of more than forty representatives of the Los Angeles County Medical Association, the woman's auxiliary, the junior section, the board of education, the University of California at Los Angeles, the College of Medical Evangelists, the health departments and other civic groups. The county society is planning to hold "The Los Angeles Health Defense Exposition" during the week at the Shrine Civic Auditorium ballroom.

**Midwinter Course on Ophthalmology and Otolaryngology.**—The Research Club of Los Angeles will open its tenth annual midwinter course in ophthalmology and otolaryngology at the Elks Club January 31. The program will include the following speakers:

Dr. Edward Jackson, Denver, Methods of Measuring Refraction.
Dr. Meyer Wiener, St. Louis, Surgery of the Globe.
Russell L. Stimson, Los Angeles, Clinical Photography of the Eyes.
Dr. Walter I. Lillie, Philadelphia, Some Practical Points Pertaining to the Routine Examination and Treatment of Patients in the Office.
Dr. Roderic P. O'Connor, Oakland, Calif., Technic of the O'Connor Operation.
Dr. Ralph I. Lloyd, Brooklyn, Perimetric Methods.
Drs. John F. Barnhill, Miami Beach, Fla., and William J. Mellinger, Santa Barbara, Points in the Anatomy That Make Surgery of the Neck Comparatively Safe and Easy.
Dr. Albert C. Furstenberg, Ann Arbor, Mich., Acute Infections of the Mouth and Pharynx.
Dr. Gilbert Roy Owen, Los Angeles, Oto-Ophthalmologic Roentgenology.
Dr. Isaac H. Jones, Los Angeles, Comments on Vitamins; Sense of Smell and Neuro-Otology.
Drs. Leland G. Hunnicutt, Russell M. Decker, Pasadena, and Herman Z. Semenov, Beverly Hills, Changes in the Mucous Membranes Resulting from Growth, Disease and Drugs; Histopathologic Changes in the Nasopharynx and Eustachian Tubes in Relation to Chronic Catarrhal Deafness, and Histopathology of the Middle Ear and Sinuses; Allergy.

## CONNECTICUT

**Changes in Health Officers.**—Dr. Clarence G. Thompson, Norwich, has been appointed health officer of Ledyard. Dr. Kenneth L. Grevatt, Saybrook, has been appointed health officer of Redding, succeeding Dr. Albert J. Trimpert. Dr. Edward P. Dunne has been named health officer of Unionville Borough, Unionville.

**Psychiatric Society Changes Name.**—The Connecticut Society for Psychiatry at a meeting in Hartford, December 11, voted to change its name to the Connecticut Society for Psychiatry and Neurology. Requirements for membership in the society were altered to make possible the admission of qualified neurologists.

**Society News.**—Dr. John S. Lockwood, Philadelphia, discussed "Progress Toward an Understanding of the Mode of Chemotherapeutic Action of the Sulfonamide Compounds" before the Yale Medical Society, New Haven, December 11.——The midwinter dinner of the Connecticut State Medical Society at the Lawn Club, New Haven, January 11, was addressed by Dr. Frank H. Lahey, Boston, President-Elect of the American Medical Association, on "Some Economic Problems by a Non-Professing Economist."

## DISTRICT OF COLUMBIA

**Course in Ocular Surgery, Pathology and Orthoptics.**—A special practical course in ocular surgery, pathology and orthoptics will be presented in Washington on April 14-18 by the resident staffs of the George Washington University School of Medicine and the Army Medical Museum. Additional information may be obtained from the Secretary, 927 Seventeenth Street N.W., Washington.

## ILLINOIS

**New Division of Social Hygiene.**—A division of social hygiene has been created in the state department of public health, the principal function of which will be to control the venereal diseases with especial emphasis on the eradication of syphilis. Dr. Herman M. Soloway, Chicago, has been made chief of the division.

**Society News.**—Dr. James E. Graham, Springfield, discussed "Varicose Veins" before the Madison County Medical Society in Edwardsville, January 3.——Dr. William Randolph Lovelace II, Rochester, Minn., discussed "The Use of Oxygen and Helium-Oxygen in Medicine and Surgery" before the Sangamon County Medical Society, Springfield, January 2.——Dr. Philip C. Jeans, Iowa City, discussed "Certain Aspects of the Nutrition of the Child" before the Rock Island County Medical Society in East Moline, January 14.

**Meeting of Bacteriologists.**—The winter meeting of the Society of Illinois Bacteriologists will be held at the Board of Trade Building, Chicago, January 31. Dinner will be followed by a program with four speakers, as follows:

Mr. H. W. Cromwell, Abbott Laboratories, North Chicago, Experiences with Microbiologic Assay of Riboflavin (Vitamin G).
Dr. Carl A. Dragstedt, Northwestern University Medical School, Chicago, Some Recent Studies in Anaphylaxis.
John C. Garey, Ph.D., University of Illinois, Urbana, The Bacteriology of Brick Cheese.
Dr. Wayne W. Fox, Northwestern University, Evanston, Laboratory Aids in Diagnosis and Treatment of Pneumonia.

### Chicago

**Professor Doisy Gives Stieglitz Lecture.**—Edward A. Doisy, Ph.D., professor and director of the department of biochemistry, St. Louis University School of Medicine, St. Louis, recently presented the first lecture under the Julius Stieglitz Memorial Lectureship at the University of Chicago. His subject was "Recent Developments in the Field of Vitamin K." The lectureship was established through joint effort of the Chicago section of the American Chemical Society and alumni of the department of chemistry of the University of Chicago.

**Joint Meeting on Otolaryngology.**—The middle section meeting of the American Laryngological, Rhinological and Otological Society in a joint session with the Chicago Laryngological and Otological Society will be addressed at the Drake Hotel, January 27, by the following:

Dr. Harry C. Rosenberger, Cleveland, Herpetiform Inflammation of the Geniculate Ganglion with Facial Paralysis: A Subjective Experience.
Dr. Samuel Iglauer, Cincinnati, Use of Preserved Human Cartilage in Reconstructive Facial Surgery.
Melvin H. Knisely, Ph.D., Chicago, Dr. Warren K. Stratman-Thomas and Theodore S. Eliot, Ph.D., Memphis, Microscopic Observations of the Changes in the Blood and Circulation in Living Animals.
Dr. William E. Grove, Milwaukee, An Evaluation of Ménière's Syndrome.
Dr. James H. Maxwell, Ann Arbor, Mich., Some Experiences with Sinusitis in the Swimmer.
Dr. Harold I. Lillie, Rochester, Minn., Suppurative Otitis Media, Acute Suppurative Labyrinthitis and Meningitis in a Pregnant Woman Near Term: Cesarean Section, Labyrinthectomy and Recovery.
Stacy R. Guild, Ph.D., Baltimore, War Deafness and Its Prevention.

Capt. Cole D. Pittman, Chanute Field, Ill., Relation of High Altitude Flying and Rapid Changes of Atmospheric Pressure to Otolaryngology and Its Effect on the Middle Ear and Accessory Sinuses in Military Aviators.
Dr. Paul H. Holinger, Chicago, Esophageal Perforations and Complications.

Dr. John Mackenzie Brown, Los Angeles, president, was introduced at this meeting.

## INDIANA

**County Secretaries' Conference.**—The Indiana State Medical Association conducted its annual secretaries' conference at the Indianapolis Athletic Club, Indianapolis, January 19. Among the speakers were:

Leo X. Smith, Indianapolis, legal adviser, Indiana Township Trustees Association, and Dr. John S. Leffel, Connersville, Administrative Problems in Care of the Indigent Sick.
Dr. Louis W. Spolyar, Indianapolis, Problems of Health in Industry.
Capt. Glen Ward, Indianapolis, The Medical Defense Program in Indiana.
Dr. Robert A. Fargher, LaPorte, Attendance at County Society Meetings.
Dr. Creighton Barker, New Haven, Conn., Everything Counts.
Drs. Norman M. Beatty and Joseph William Wright, Indianapolis, Current Legislation.

Roundtable discussions were conducted on the following topics: What are county societies doing as to membership of men in military service?; types of membership; when and how to transact routine society business and membership of the colored physician.

## LOUISIANA

**Changes in Hospital Superintendents.**—Dr. Joseph O. Weilbaecher Jr. has been appointed acting director of Charity Hospital, New Orleans. He succeeds Dr. Roy W. Wright, resigned. Dr. Frank A. Donaldson, assistant superintendent of the Mississippi State Hospital, Whitfield, has been named superintendent of the East Louisiana Hospital for the Insane, Jackson. He succeeds Dr. Eugene M. Robards Jr., who became acting superintendent on the recent death of Dr. Charles S. Miller, who also served as acting superintendent. Dr. John T. Crebbin, Shreveport, has been elected superintendent of the Eye, Ear, Nose and Throat Hospital, New Orleans. Dr. Richard F. Gates, Hammond, was recently named superintendent of the Florida Parishes Charity Hospital, Independence.

**Society News.**—Recently elected officers of the Tri-State Medical Society of Texas, Louisiana and Arkansas, chosen at the meeting in Shreveport, include Drs. Rufus B. Robins, Camden, Ark., president; Spencer Allen Collom Jr., Texarkana, vice president from Texas; Robert T. Lucas, Shreveport, vice president from Louisiana; Joe F. Rushton, Magnolia, vice president from Arkansas, and William Hibbitts, Texarkana, Texas, secretary-treasurer. The 1941 convention will be in Texarkana.——Dr. Francis E. LeJeune, New Orleans, discussed "Hoarseness" before the LaFourche Valley Medical Society in Raceland, December 18.——The Orleans Parish Medical Society was addressed in New Orleans, December 9, by Drs. Daniel N. Silverman and Robert A. Katz on "Plasma Therapy" and Idys Mims Gage, "Use of Plasma in Surgical Practice."

## MICHIGAN

**County Secretaries' Conference.**—The Michigan State Medical Society held its annual county secretaries' conference at Lansing, January 19. Dr. Horace Wray Porter, Jackson, chairman of secretaries, presided, and Dr. Harold W. Wiley, Lansing, president of the Ingham County Medical Society, delivered the address of welcome. The speakers included:

Dr. L. Fernald Foster, Bay City, The Future in Legislation.
Dr. Henry R. Carstens, Detroit, Michigan Medical Service.
Lieut. Col. Harold A. Furlong, Lansing, Medical Preparedness.
H. Van Y. Caldwell, Cleveland, How to Make Your County Medical Society More Influential and Successful.

The afternoon session was held in conjunction with a meeting of the state and county health officers and speakers were:

Dr. Kenneth E. Markuson, Lansing, Industrial Health in Relation to National Defense.
Dr. Wyman C. C. Cole, Detroit, Immunization Schedule.
Dr. Arthur W. Newitt, Lansing, Tuberculosis Case Finding.
Dr. Loren W. Shaffer, Detroit, New Five-Day Treatment for Syphilis.

The honor guest at the noonday dinner was Lieut. Gov. Frank Murphy, who addressed the group on "Michigan's New Intangibles Tax Law."

## MINNESOTA

**Society News.**—At the December meeting of the Meeker County Medical Society in Litchfield, plans for the project for eradication of tuberculosis in the county were discussed by members of the committee on control of tuberculosis of the Minnesota State Medical Association, including Drs. Jay Arthur Myers and Chester A. Stewart, Minneapolis; Edward A. Meyerding, St. Paul; Herbert A. Burns, Ah-gwah-ching, and Bertram S. Adams, Hibbing.

**Personal.**—Dr. Daniel C. Lochead, deputy city health officer of Rochester for sixteen years, has resigned, effective April 14. Dr. Floyd M. Feldman, director of rural health of district number 3 of the state board of health with headquarters in Rochester, has been appointed part time deputy, effective January 1.——Dr. Karl H. Pfuetze, Nopeming, has been named superintendent of the Mineral Springs Sanatorium, Cannon Falls, succeeding Dr. William D. Beadie, who resigned because of ill health.

**Dr. Rous Will Present Christian Lecture.**—Dr. Francis Peyton Rous of the Rockefeller Institute for Medical Research will deliver the tenth annual George Chase Christian Lecture at the University of Minnesota Medical School, Minneapolis, February 5. His subject will be "Present Knowledge of Carcinogenesis." At a luncheon roundtable on the same day Dr. Rous will discuss "Latent Neoplastic Changes and Conditional Tumors." Tentative plans are being made for Dr. Rous to participate in a seminar on cancer to be arranged by Dr. Elexious T. Bell, Minneapolis, of the Cancer Institute Committee.

**Portrait of Dr. Litzenberg.**—A portrait of Dr. Jennings C. Litzenberg, Minneapolis, professor emeritus of obstetrics and gynecology, University of Minnesota Medical School, was unveiled at a dinner at the Minneapolis Club December 19 and presented to the university. Guy Stanton Ford, Ph.D., president of the university, received the gift. The portrait was painted by Edward Brewer of St. Paul. A native of Waubeck, Iowa, Dr. Litzenberg graduated at Minnesota in 1899. He joined the staff of his alma mater in 1907 as assistant professor of obstetrics. He was associate professor from 1910 to 1914, when he became professor and chief of the department. Dr. Litzenberg has served as president of the Hennepin County Medical Society, of the American Association of Obstetricians and Gynecologists and of the Minnesota Academy of Medicine, and has contributed extensively to the literature of his specialty. He became professor emeritus in 1938.

## NEW YORK

**Personal.**—Dr. Eric Ponder, director of the Biological Laboratory of the Long Island Biological Association at Cold Spring Harbor for the past five years, has resigned, and Millislav Demerec, Ph.D., of the department of genetics, Carnegie Institution of Washington, Cold Spring Harbor, was elected director for the year 1941. Mr. Arthur W. Page, president of the association, also resigned because of the pressure of other duties, and Robert Cushman Murphy, Sc.D., curator of oceanic birds at the American Museum of Natural History, was elected to succeed him.

**Society News.**—Dr. Benjamin J. Slater, Rochester, addressed the quarterly meeting of the Ontario County Medical Society in Canandaigua, January 14, on occupational diseases.——Dr. Sydney W. Stringer addressed the Onondaga County Medical Society, Syracuse, January 7, on "Recent Advances in Sex Hormones."——Dr. Ferdinand J. Schoeneck, addressed the Syracuse Obstetrical Society, January 14, on "The Effect of Smoking on Pregnancy."——Dr. Richard B. Phillips, Rochester, Minn., addressed the Orleans County Medical Society, Albion, December 19, on "Recent Advances in Anesthesia."——Dr. Severo E. Barrera, New York, discussed "Electric Shock Therapy in Mental Disorders" at a meeting of the Dutchess County Psychiatrical Society at the Harlem Valley State Hospital, Wingdale, November 28.——Dr. Charles Edwin Woods, Westbury, addressed the Medical Society of the County of Nassau, Garden City, November 26, on "A New Maneuver for Shoulder Delivery."

### New York City

**Janeway Lecture at Mount Sinai.**—Dr. William B. Castle, professor of medicine, Harvard Medical School, Boston, delivered the Edward Gamaliel Janeway Lecture at Mount Sinai Hospital, January 24. Dr. Castle's subject was "Hemolytic Anemias."

**Fourth Harvey Lecture.**—Carl C. Speidel, Ph.D., professor of anatomy, University of Virginia Department of Medicine, Charlottesville, delivered the fourth Harvey Lecture of the current series at the New York Academy of Medicine, January 16. His subject was "Adjustments of Nerve Endings."

**Alumni Meeting Date Changed.**—The Annual Alumni Day at New York University College of Medicine will be held March 21 and 22 instead of on February 22 as in previous

years, it is announced. There will be a dinner the first evening and the following day will be devoted to a scientific program. There will be a luncheon Saturday, March 22, with Dr. Nathan B. Van Etten, President of the American Medical Association, as the guest speaker.

**Tuberculosis Hospital Opened.**—The new Triboro Tuberculosis Hospital in Jamaica, borough of Queens, was opened January 1. The new institution will serve principally the Bronx, Queens and Brooklyn. The building, which will ultimately care for 557 patients, is designed to provide a maximum of sunlight. On the patients' floors the outside walls have large areas of glass; the wards are separated by glass partitions and all open directly on balconies. The cost of the hospital was about $3,500,000, of which 45 per cent was provided by a PWA grant. Dr. Alfred Ring is the superintendent.

## NORTH CAROLINA

**Seaboard Medical Association Meeting.**—Dr. Waverly R. Payne, Newport News, Va., was elected president of the Seaboard Medical Association at its forty-fifth annual meeting in Washington, December 3-5; Drs. George Erick Bell, Wilson, Wilbert E. Butler, Norfolk, Va., and Plummer A. Nicholson, Washington, were elected vice presidents, and Dr. Clarence Porter Jones, Newport News, Va., was reelected secretary. The speakers included:

Dr. Norris W. Vaux, Philadelphia, The Maternal Pelvis in Relation to Labor.
Dr. James P. Hennessy, New York, Ureteroplacental Apoplexy.
Dr. Julian L. Rawls, Norfolk, Va., The Response of Intrathoracic Tumors to Irradiation.
Dr. Francis Bayard Carter, Durham, N. C., Mycotic Infection in Obstetric and Gynecologic Patients.
Dr. Oscar Swineford Jr., Charlottesville, Va., Asthma and Heart Disease.
Dr. Rachel D. Davis, Kinston, Intradermal Smallpox Vaccines.

**Appointments to Bowman Gray School of Medicine.**—The trustees of Wake Forest College recently announced the following appointments, among others, to the faculty of the new Bowman Gray School of Medicine of Wake Forest in Winston-Salem:

Dr. James P. Rousseau, Winston-Salem, professor of radiology.
Dr. John A. Rose, Philadelphia, associate professor of psychiatry.
Dr. Frank R. Lock, New Orleans, associate professor of obstetrics and gynecology.
Dr. Nelson M. Webster, Winston-Salem, assistant professor of obstetrics and gynecology.
James Maxwell Little, M.S., Nashville, Tenn., assistant professor of physiology and pharmacology.

Dr. Rose will also be in charge of a child guidance clinic to be established under the sponsorship of the Junior League, the Winston-Salem Mental Hygiene Society and the new medical school. He has recently been on the staff of the Philadelphia Child Guidance Clinic and on the staff of the Institute for Mental Hygiene of the Pennsylvania Hospital.

## OHIO

**Annual Library Meeting.**—Dr. John F. Fulton, Sterling professor of physiology, Yale University School of Medicine, New Haven, Conn., was the guest speaker at the annual meeting of the Cleveland Medical Library Association, January 17. His subject was "The Life of Harvey Cushing."

**The Bunts Lecture.**—Lowell J. Reed, Ph.D., professor of biostatistics and dean, Johns Hopkins University School of Hygiene and Public Health, Baltimore, delivered the Frank E. Bunts Lecture at the Cleveland Clinic, January 8. His subject was "The Place of Statistical Method in Medical Science."

**Conference of Health Officers.**—The twenty-first annual conference of health commissioners of Ohio was held in Columbus, December 12-13. The speakers included Drs. Erval R. Coffey, U. S. Public Health Service, Washington, D. C., on "Environmental Sanitation"; Walter M. Simpson, Dayton, "Tularemia" and Ray S. Dixon, Detroit, "The Local Health Officer's Approach to the Control of Syphilis."

**Personal.**—Dr. Albert R. Smith, Iowa City, has been appointed orthopedist to the medical section of the state industrial commission, succeeding Dr. Clyde W. Dawson, Columbus, who resigned to enter private practice.——Dr. Eli R. Crew has resigned as superintendent of the Miami Valley Hospital, Dayton, after twenty-eight years in the position. His resignation will become effective when his successor is chosen, according to *Hospitals*.

## OKLAHOMA

**Lecture in Memory of Dr. Long.**—Dr. Ernest Sachs, professor of clinical neurologic surgery, Washington University School of Medicine, St. Louis, will deliver the first Leroy Long Memorial Lecture at the University of Oklahoma School of Medicine, Oklahoma City, February 2. Dr. Sachs' subject will be "Surgery of Brain Tumors Today and Ten Years Ago." The lecture is sponsored by the Phi Beta Pi fraternity.

## WASHINGTON

**Society News.**—Dr. Marion M. Kalez addressed the Spokane County Medical Society, Spokane, December 12, on "Recent Advances in Aviation Medicine."——Dr. Christian R. Goodhope, Garfield, addressed the Whitman County Medical Society, January 9, in Colfax on heart disease.——Dr. Roger Anderson, Seattle, discussed treatment of sore and tender feet at a meeting of the Walla Walla Valley Medical Society, Walla Walla, December 12.

## GENERAL

**Special Society Elections.**—New officers of the Central Society for Clinical Research include Drs. Lawrence D. Thompson, St. Louis, president; Arlie R. Barnes, Rochester, Minn., vice president, and Carl V. Moore, St. Louis, secretary-treasurer. The society held its annual meeting on November 1-2 at the Drake Hotel in Chicago.——Dr. Richard S. Weiss, St. Louis, was chosen president of the American Academy of Dermatology and Syphilology at its annual meeting in Chicago, December 16. Other officers include Drs. John G. Downing, Boston, vice president; Earl D. Osborne, Buffalo, secretary and director, and Clyde L. Cummer, Cleveland, treasurer.

**Report of Foundation for Infantile Paralysis.**—The National Foundation for Infantile Paralysis, which derives its funds chiefly from the celebrations sponsored annually by the Committee for the Celebration of the President's Birthday on January 30, has issued its annual report. The National Foundation operates in two fields: the national field, in which it has so far acted principally as a grant-making agency, and the local field, through chapters now organized in more than 1,300 counties. The national activities cover five divisions: virus research, nutritional research, research on after-effects, epidemics and education. For studies on the virus the foundation has appropriated $116,311.34 to various university and hospital investigators. A grant of $37,500 was made to the University of Texas Faculty of Medicine, Galveston, for a study of the principles of nutrition and their application to the entire field of infectious diseases. It is believed that the broad approach is desirable in order that tools and methods of investigation may be developed before the specialized field is studied. Research on methods of reducing the impairment caused by infantile paralysis is being advanced by grants and appropriations totaling $108,319.50. The work includes studies of hospital care, comparison of various methods of treatment and the entire problem of the manufacture and use of braces. The foundation's work in education includes not only dissemination of information to the public but provision for fellowships for young physicians, five for orthopedic surgeons and five for students of virus diseases. Grants have also been made for the training of orthopedic nurses and for establishment and expansion of courses to train them. A graduate school at the Georgia Warm Springs Foundation for the training of physical therapists is planned and lectures for physicians are in prospect. Pamphlets describing the use of respirators and "Toronto" splints, and one on nursing care of patients have been issued. For the educational activities grants and appropriations amounted to $189,562.54. Epidemiologic studies were made during epidemics at Tacoma, Wash., and Detroit and in Indiana. In 1939 splints and frames were supplied to epidemic areas in New York and South Carolina and as a result the foundation has established a central supply depot in New York from which splints and frames have been shipped to all parts of the country. Recently a survey has been undertaken on the use of respirators. To carry out this work in epidemiology and epidemics, the foundation appropriated $82,778.48. During the year ended Sept. 30, 1940, the foundation received a cash income of $688,800.71, of which $620,611.63 represented 50 per cent of the net proceeds of the 1940 Birthday Celebrations. The sixty-three grants and appropriations for the year amounted to $709,471.68.

Local activities are financed by the remaining 50 per cent of the net proceeds of the Birthday Celebrations, which for the fiscal year ended Sept. 30, 1940, amounted to $779,592.16. Under the supervision of the national organization the chapters give direct assistance to victims. During epidemics of last summer the chapters that were ready to meet the emergency gave splendid assistance not only to the victims but to the medical profession and the public health officers, the report said.

# Foreign Letters

## LONDON

*(From Our Regular Correspondent)*

Nov. 23, 1940 (delayed).

### Treatment of War Burns

At the Royal Society of Medicine, Surgeon Rear Admiral Wakeley opened a discussion on the treatment of war burns. At the outbreak of war it was thought that the treatment would be simple, and the use of tannic acid was regarded as completely satisfactory. But this proved far from true in the navy, where many casualties from burns occurred. War burns differed from those of civilian life in that they might not be treated for many hours or even days. On a warship only first aid treatment could be given in the majority of cases. Most of the burns involved the face and hands and were due to gun flash, bomb flash, incendiary bombs or gasoline. First aid treatment consisted in morphine, warmth and fluid to counteract shock. If this was marked, plasma transfusion was given. Secondary shock occurred some hours after the burn and accounted for 80 per cent of the deaths. The most important factor in it was the loss of plasma from the burned surface. The blood might be so concentrated that the hemoglobin rose to 140 per cent. The best treatment was to replace the plasma protein. Given intravenously, plasma raised the osmotic pressure sufficient to restore the normal distribution of fluid between the vascular and interstitial components. Whole blood transfusion and intravenous physiologic solution of sodium chloride or sterile water were contraindicated. The amount of plasma necessary must be estimated by frequent blood examinations.

Wakeley agreed with Aldrich that acute toxemia from burns was due to streptococcic infection. It did not appear for several days and could be prevented by primary cleansing before coagulation. It was not nearly so common as in the last great war, for which no doubt coagulation was responsible. For extensive burns with toxemia, saline baths had proved valuable. In first or second degree burns, sepsis could be prevented if coagulation treatment was given at once and adequate cleansing and coagulation followed on arrival at a hospital.

With regard to local treatment, he favored gentian violet jelly with merthiolate (1:5,000), which could be applied to the burned areas without any cleansing. The application should be liberal, for it was painless and even soothing. It would seal off the burned area and formed a crust which remained until arrival at a hospital. Local treatment should not be given in the presence of shock. Tannic acid should not be used on the hands and face.

In the hospital the treatment of shock was instituted, and plasma banks and dried plasma were playing an important part. Oxygen administration was helpful. After shock had been treated the patient was taken to a warm room and anesthetized with gas and oxygen. The burned area was thoroughly cleansed with saline solution, dried with an electric hair drier and two applications of an aqueous solution of triple dye (2 per cent gentian violet, 1 per cent brilliant green and 0.1 per cent acriflavine) sprayed on the surface. This produced a thin, supple, adherent tan, which loosened about the eighth day and gradually fell off, leaving a healed area. If the burn was extensive and of third degree, the area should be excised and skin grafted.

Prof. W. C. Wilson said that coagulation treatment was used in secondary shock to minimize exudation, which it did. It also relieved pain. Whatever the cause of the acute toxemia, which was still unknown, it had become less common since coagulation treatment was instituted. Whether this was due to inhibition of bacterial growth was uncertain. Sepsis occurred predominantly in a deeply burned area, and the object of coagulation, which did not penetrate more than a millimeter of tissue, was to make the conditions for bacterial growth as unsuitable as possible. This was done more effectively by coagulation than by any other form of local treatment.

Mr. A. H. McIndoe said that coagulation, so useful in preventing toxemia, had been carried too far, particularly when there was no evidence of toxemia. This held especially for tannic acid. In first or second degree burns, coagulation gave excellent results. But where the loss of skin was complete coagulation usually failed, particularly in regard to ultimate function. In these cases it was impossible to tan or coagulate the entire area. A heavily infected granulating surface was exposed in which healing might be slow and painful, and during this phase the patient might become wasted and anemic from chronic sepsis. Under the unyielding tannic acid, edema could develop to a degree which produced further deformity. In third degree cases treatment should be directed toward obtaining the best granulating surface for skin grafting. He showed slides illustrating the value of a thermostatically controlled saline bath, followed by saline packs and later by Thiersch grafts.

### The Indispensable Corset

One of the measures of our war effort is the reduction of avoidable buying, such as of clothes, which the government enforces by reducing the quantity that wholesale dealers are allowed to supply to retailers. The object is to divert industry into war production as much as possible. But an order by the board of trade reducing the supply of corsets by half has brought trouble. The order was discussed by a meeting of press women at which no one agreed that corsets were a luxury. It was stated that 95 per cent of women out of their teens depend on a corset for support and comfort. A woman physician said that it was obvious that no woman was consulted in the matter. But the meeting seems to have ignored the point that the object of such orders is not to prevent the use of articles of attire but to promote economy by the wearing of old ones, which are often discarded for the sake of appearance—a thing which should be ignored to help the war effort.

### Mosquitoes a War Danger

In the last great war precautions against the spread of malaria to England were found necessary because soldiers returned from malarial districts and were bitten by mosquitoes in this country. These mosquitoes became infected and thus spread the disease. As the same may occur in this war, the Ministry of Health has published a "Memorandum on Measures for the Control of Mosquito Nuisances in Great Britain," by Lieutenant Colonel Sinton and Mr. P. G. Shute. This memorandum gives a full account of the types of mosquito encountered in this country, of the reactions between mosquitoes and disease and of the measures to be taken to bring the mosquitoes under control.

# Marriages

JAMES WILLIAM WARD, Amarillo, Texas, to Miss Nancy Elizabeth Edwards of Nashville, Tenn., recently.

THEODORE WILLIAM WITALIS, Pomona, Calif., to Miss Betty Jane McPherson at Yuma, Ariz., Nov. 21, 1940.

JOHN H. ROBINSON III, Spartanburg, S. C., to Miss Betty Watson of Portsmouth, Va., in November 1940.

WILLIAM RICHARD SNELLING to Miss Julia Adella Meserve, both of Fernandina, Fla., in September 1940.

CLAUD WALTER PERRY JR. to Miss Marie Katherine Jenkins, both of Chattanooga, Tenn., Sept. 14, 1940.

THOMAS L. LAUDERDALE JR. to Miss Margaret Hornberger, both of Fort Worth, Texas, Nov. 20, 1940.

JAMES BISHOP BLODGETT, Detroit, to Miss Eleanor Fisher Clark of Bronxville, N. Y., Sept. 14, 1940.

# Deaths

**Paul Nicholas Leech, Ph.D.,** Director of the Division of Foods, Drugs and Physical Therapy in the headquarters office of the American Medical Association, died suddenly January 14 following a hemorrhage of the brain. He had suffered for some time with arterial hypertension. Dr. Leech was born in Oxford, Ohio, Aug. 12, 1889 and obtained his A.B. degree from Miami University, Oxford, Ohio, in 1910 and received the degree of master of science from the University of Chicago in 1911 and the Ph.D. in 1913. He also held the honorary degree of master of pharmacy from the Philadelphia College of Pharmacy. From 1911 to 1913 he was assistant in the Department of Chemistry at the University of Chicago, working with Prof. Julius Stieglitz. In 1913 he joined the staff of the American Medical Association as a chemist and in 1923 became director of the chemical laboratory, working under Prof. W. A. Puckner, who was the Secretary of the Council on Pharmacy and Chemistry. Following the death of Professor Puckner in 1932 Dr. Leech became Secretary of the Council on Pharmacy and Chemistry, and when the Board of Trustees created the Division of Foods, Drugs and Physical Therapy he was appointed director.

PAUL NICHOLAS LEECH, PH.D.
1889-1941

In 1918 Dr. Leech served as a lieutenant in the Sanitary Corps of the United States Army. He was a member of the American Chemical Society, a councilor from 1922 to 1936 and a director from 1928 to 1934. He also served as chairman of the Chicago section of the American Chemical Society in 1926. He was a member of the Chicago Chemists Club and trustee from 1925 to 1932. His contributions to medicine were recognized by associate fellowship in the American Medical Association and membership in the Institute of Medicine of Chicago. He was a member of Sigma Xi and an honorary member of Phi Beta Kappa. During his university career Dr. Leech contributed to research in the fields of formic acid, molecular rearrangements, medicinal chemistry and drug development. In his position as Secretary of the Council on Pharmacy and Chemistry, he served as an associate editor of many publications dealing with drugs, vitamins, glandular products and pharmacy. On several occasions he represented the American Medical Association in the United States Pharmacopeial Convention. For more than a quarter of a century Dr. Leech rendered devoted service to the physicians of this country and earned for himself a nationwide reputation for integrity, scientific judgment and the highest ideals in the advancement of pharmacy and chemistry.

**Magnus A. Tate,** Cincinnati; Medical College of Ohio, Cincinnati, 1891; member of the Ohio State Medical Association; member of the House of Delegates of the American Medical Association from 1923 to 1928; formerly associate professor of clinical obstetrics, University of Cincinnati College of Medicine; past president of the Cincinnati Obstetrical Society and the Cincinnati Academy of Medicine; formerly vice president and secretary of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons; fellow of the American College of Surgeons; at various times on the staffs of Speer's Memorial Hospital, Dayton, Ky., Cincinnati General and St. Mary's Hospital; aged 72; died, Dec. 7, 1940.

**Allan Lockhart McLean,** Halifax, N. S., Canada; Dalhousie University Faculty of Medicine, Halifax, 1926; professor of epidemiology at his alma mater; at one time associate in preventive medicine, Medical College of Virginia, Richmond; formerly health officer of Southampton County and Henrico County, Va.; at one time secretary of the Virginia Public Health Association; aged 44; died, Oct. 25, 1940.

**Charles Edward Duffin,** Jeffersonville, Ind.; Kentucky School of Medicine, Louisville, 1903; member of the Indiana State Medical Association; veteran of the Spanish-American and World wars; formerly served with the United States Public Health Service; at one time health officer of Richmond; aged 60; died, Nov. 21, 1940, in the Veterans Administration Facility, Marion.

**Hiram Bradbury Tebbetts,** Los Angeles; University of Southern California College of Medicine, Los Angeles, 1904; past president of the Los Angeles Obstetrical Society; served during the World War; formerly professor of physiology at the College of Dentistry, University of Southern California; for many years on the staff of St. Vincent's Hospital; aged 62; died, Nov. 26, 1940.

**George Otto Pobe** ✠ Port Jervis, N. Y.; Long Island College Hospital, Brooklyn, 1901; fellow of the American College of Surgeons; for many years health officer of Port Jervis and the town of Deer Park; aged 65; consulting surgeon to the Callicoon (N. Y.) Hospital; surgeon to the Deerpark Hospital, where he died, Dec. 4, 1940, of arteriosclerosis.

**Edmund Waring Simons,** Summerville, S. C.; Medical College of the State of South Carolina, Charleston, 1905; member of the South Carolina Medical Association; served with the United States Public Health Service during the World War; for many years member of the school board; aged 73; died, Nov. 17, 1940.

**Jacob Tyree Woodson** ✠ West Hartford, Conn.; Columbia University College of Physicians and Surgeons, New York, 1920; served during the World War; on the staffs of the Hartford Hospital and the Municipal Hospital; aged 47; died, Nov. 9, 1940, of rheumatic heart disease and acute respiratory tract infection.

**Thomas Vincent Golden,** Clarinda, Iowa; John A. Creighton Medical College, Omaha, 1910; served during the World War; formerly health officer of Creston; on the staff of the Clarinda State Hospital; aged 53; died, Nov. 21, 1940, in the Veterans Administration Facility, Des Moines, of peritonitis.

**William Van Vorst Parramore,** Cochran, Ga.; University of Maryland School of Medicine, Baltimore, 1910; at one time medical superintendent of the State Tuberculosis Sanatorium, Alto; aged 56; was killed, Nov. 27, 1940, when the automobile in which he was driving was struck by a train.

**Joseph Egbert Pollard,** Chatham, N. J.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1894; served during the World War; formerly associate medical director of the Prudential Insurance Company; aged 70; died, Nov. 29, 1940, in Clearwater, Fla.

**Charles Carlin Ayres,** White Hall, Md.; University of Maryland School of Medicine, Baltimore, 1914; member of the Medical and Chirurgical Faculty of Maryland; served during the World War; aged 48; died, Dec. 9, 1940, in the Maryland General Hospital, Baltimore, of cerebral hemorrhage.

**Corden Thorne Graham,** Rochester, N. Y.; University of Michigan Homeopathic Medical School, Ann Arbor, 1904; member of the Medical Society of the State of New York; served during the World War; aged 59; died, Nov. 26, 1940, in the Veterans Administration Facility, Batavia.

**Dorrance Ellsworth Sheffield,** St. Johnsbury, Vt.; University of Vermont College of Medicine, Burlington, 1923; member of the Vermont State Medical Society; served during the World War; aged 41; died, Nov. 24, 1940, in the Brightlook Hospital of coronary occlusion.

**Robert Cordner,** Middletown, N. Y.; Columbia University College of Physicians and Surgeons, New York, 1905; member of the Medical Society of the State of New York; at one time school physician; physician on the steamship *Panama;* aged 67; died in November 1940.

**Arthur Norman Clark,** South Norwalk, Conn.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1883; aged 80; died, Nov. 25, 1940, in the Norwalk Hospital of carcinoma of the ascending colon with metastasis to the liver.

**George Davis Vick,** Selma, N. C.; Jefferson Medical College of Philadelphia, 1906; member of the Medical Society of the State of North Carolina; member of the school board; aged 63; died, Nov. 2, 1940, of coronary occlusion, hypertension and arteriosclerosis.

**Will Foster Fyke,** Springfield, Tenn.; Vanderbilt University School of Medicine, Nashville, 1918; member of the Tennessee State Medical Association; secretary of the Robertson County Medical Society; aged 50; died, Nov. 27, 1940, of cardiorenal disease.

**Ira Raymond Willits** ✠ Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1905; aged 58; died, Dec. 3, 1940, in St. Mary's Hospital, Galesburg, Ill., of hypertensive heart disease and chronic nephritis.

**Theodore B. Fulper,** Hampton, N. J.; Jefferson Medical College of Philadelphia, 1889; member of the Medical Society of New Jersey; formerly medical inspector for the schools and a member of the board of health; aged 73; died, Nov. 15, 1940, of uremia.

**Louis Harward Webb,** Sunmount, N. Y.; Jefferson Medical College of Philadelphia, 1910; served during the World War; served with the Veterans Administration for many years; manager of the Veterans Administration Facility; aged 52; died, Nov. 12, 1940.

**Henry Russell Hitchcock,** Plymouth, Mass.; Harvard Medical School, Boston, 1890; member of the Massachusetts Medical Society; formerly served with the United States Public Health Service; aged 79; died, Nov. 23, 1940, of cerebral hemorrhage.

**Charles Lawrence Weiher,** Poughkeepsie, N. Y.; Bellevue Hospital Medical College, New York, 1885; member of the Medical Society of the State of New York; aged 81; died, Nov. 18, 1940, in the Vassar Brothers Hospital of angina pectoris.

**John Henry Rose** ✠ Kansas City, Kan.; University of Kansas School of Medicine, Kansas City, 1906; for many years police surgeon; aged 63; died, Nov. 26, 1940, in St. Margaret's Hospital of pneumonia after an operation for appendicitis.

**Clifford Dennison Hamrick** ✠ Passed Assistant Surgeon Lieutenant, United States Navy, San Diego, Calif.; Emory University School of Medicine, Atlanta, Ga., 1930; entered the navy in 1930; aged 40; died, Nov. 27, 1940, of pneumonia.

**Earle J. Brashear,** North Pleasureville, Ky.; Hospital College of Medicine, Louisville, 1898; aged 65; died, Nov. 27, 1940, in the Pewee Valley Sanitarium and Hospital, Pewee Valley, of bleeding peptic ulcer with secondary anemia.

**Charles Frederick Voigt** ✠ Midway, Ky.; University of Louisville (Ky.) Medical Department, 1915; past president and secretary of the Woodford County Medical Society; served during the World War; aged 47; died, Nov. 19, 1940.

**Benjamin Wise Burt,** Holly Springs, N. C.; College of Physicians and Surgeons, Baltimore, 1886; member of the Medical Society of the State of North Carolina; aged 78; died, Nov. 14, 1940, of arteriosclerotic heart disease.

**Francis David John Chippendale,** Fall River, Mass.; Georgetown University School of Medicine, Washington, D. C., 1936; member of the Massachusetts Medical Society; aged 28; died, Nov. 19, 1940, of subacute endocarditis.

**Karl L. Thorsgaard** ✠ Chicago; Rush Medical College, Chicago, 1900; served in various capacities on the staffs of the Augustana Hospital and the American Hospital; aged 65; died, Nov. 24, 1940, of coronary thrombosis.

**Henri Gedeon Coupal,** Montreal, Que., Canada; M.B., School of Medicine and Surgery of Montreal, Faculty of Medicine of the University of Laval at Montreal, 1908, and M.D. in 1910; aged 55; died, Nov. 2, 1940.

**Thomas Hightower Hancock,** Atlanta, Ga.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1891; member of the Medical Association of Georgia; aged 71; died, Nov. 17, 1940.

**Leon Clifford Wills,** Philadelphia; Jefferson Medical College of Philadelphia, 1907; member of the Medical Society of the State of Pennsylvania; aged 58; died, Nov. 10, 1940, of cerebral thrombosis and arteriosclerosis.

**Henry Claiborne McCullough** ✠ Town Creek, Ala.; Medical College of Alabama, Mobile, 1905; president of the Lawrence County Medical Society; aged 63; died, Nov. 8, 1940, of carcinoma of the parotid gland.

**Clarence Curtin Bobb** ✠ Lykens, Pa.; Temple University School of Medicine, Philadelphia, 1919; served during the World War; aged 45; died, Nov. 16, 1940, in St. Joseph Hospital, Reading, of coronary occlusion.

**Charles Merritt Ausley,** Tallahassee, Fla.; Baltimore Medical College, 1901; for many years member of the board of county commissioners; aged 61; died, Nov. 22, 1940, of bronchopneumonia and arthritis.

**Virgil Eugene Franklin,** Graymont, Ga.; University of Maryland School of Medicine, Baltimore, 1896; member of the Medical Association of Georgia; aged 70; died, Nov. 13, 1940, of cerebral hemorrhage.

**Frank Alvin Rogers,** Boston; Medical School of Maine, Portland, 1876; member of the Massachusetts Medical Society; formerly health officer and school physician in Everett; aged 85; died, Nov. 15, 1940.

**Thomas J. Fleming** ✠ Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1894; on the staff of St. Joseph's Hospital; aged 68; died, Nov. 23, 1940, of coronary thrombosis.

**Edward James O'Rourke** ✠ Cambridge, Mass.; Tufts College Medical School, Boston, 1909; on the staff of the Cambridge City Hospital; aged 54; died, Nov. 20, 1940, of coronary heart disease.

**Walter Clarence Friday,** Starkville, Miss.; Memphis (Tenn.), Hospital Medical College, 1913; served during the World War; aged 49; died, Nov. 15, 1940, of bilateral pulmonary tuberculosis.

**Clyde Edward Cox** ✠ Worcester, Mass.; Harvard Medical School, Boston, 1930; on the staffs of the City Hospital and the Fairlawn Hospital; aged 35; died, Nov. 10, 1940, of acute coronary occlusion.

**Terry Augustus Walter,** Portland, Maine; Hahnemann Medical College and Hospital of Philadelphia, 1914; served during the World War; aged 59; died, Nov. 23, 1940, of coronary occlusion.

**William Harrison Floyd** ✠ Jena, La.; Memphis (Tenn.) Hospital Medical College, 1910; aged 55; died, Nov. 21, 1940, in the Baptist Hospital, Alexandria, of carcinoma of the head of the pancreas.

**Jennie Elizabeth Mabee,** Poughkeepsie, N. Y.; Cornell University Medical College, New York, 1923; member of the Medical Society of the State of New York; aged 43; died, Nov. 7, 1940.

**D. Ross Hinton,** Start, La.; University of Tennessee College of Medicine, Memphis, 1914; aged 53; died, Nov. 23, 1940, in a hospital at Monroe of acute rheumatic fever and influenza.

**Jesse Lee Cook,** Oxford Junction, Iowa; Keokuk (Iowa) Medical College, College of Physicians and Surgeons, 1900; aged 64; died, Nov. 2, 1940, in Cedar Rapids of diabetes mellitus.

**Thomas A. Irwin,** Franklin, Pa.; Chicago Homeopathic Medical College, 1888; member of the Medical Society of the State of Pennsylvania; aged 78; died, Dec. 5, 1940, of heart disease.

**Egbert Frederick Henderson,** Edmonton, Alta., Canada; McGill University Faculty of Medicine, Montreal, Que., 1921; served during the World War; aged 49; died, Oct. 29, 1940.

**Leo Strousse,** Philadelphia; Jefferson Medical College of Philadelphia, 1906; on the staff of the Jewish Hospital; aged 55; died, Nov. 30, 1940, of chronic myocarditis and nephritis.

**Paul B. Waldman,** Reading, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1884; aged 82; was found dead, Nov. 19, 1940, of heart disease.

**Andrew J. Cook,** Flora, Ind.; Eclectic Medical Institute, Cincinnati, 1884; aged 81; died, Nov. 19, 1940, of cerebral hemorrhage and arteriosclerosis.

**Frank Virgil Willard,** Loveland, Colo.; University of Colorado School of Medicine, Denver, 1938; aged 29; died in November 1940 of meningitis.

**Cora E. Alcorn,** Spokane, Wash.; Central Medical College of St. Joseph, Mo., 1900; aged 68; died, Nov. 29, 1940, of carcinoma of the breast.

**Eugene Warren,** East Cleveland, Ohio; Chicago Homeopathic Medical College, 1894; aged 70; died, Nov. 11, 1940, of cerebral hemorrhage.

**James L. Gray,** Chicago; Hering Medical College, Chicago, 1907; aged 82; died, Nov. 29, 1940, in St. Bernard's Hospital of tetanus.

**Joseph J. Rosenberg,** New York; University and Bellevue Hospital Medical College, New York, 1903; aged 59; died, Nov. 6, 1940.

# Correspondence

## USE OF POWDERED CRYSTALLINE SULFANILAMIDE IN SURGERY

*To the Editor:*—In the Nov. 16, 1940 issue of THE JOURNAL, the local use of sulfanilamide is discussed in an editorial. Reference was made of its use in solution as a direct irrigation of the wound in cases of combined abdominoperineal or posterior resection of the rectum. During the past year at the Roosevelt Hospital we have been using the powdered crystalline sulfanilamide directly in the peritoneal cavity at the time of operation.

On Jan. 10, 1940 I used the crystalline drug locally in the peritoneal cavity in a critical case of diffuse peritonitis due to a ruptured appendix. Shortly after the recovery of this patient, its local peritoneal use became routine at Roosevelt Hospital in cases of abdominal infection and it was used also prophylactically in certain types of intestinal resection. To date 175 patients have been treated in this manner with excellent results. Of the 175 cases of all kinds, 55 were those of abscess and peritonitis following ruptured appendixes; 8 of the cases of peritonitis were considered to be of the diffuse variety and the condition at, or before, operation was considered to be critical. Deaths did not occur in this group of 55 cases.

The group of cases in which drainage was done was remarkable for the rapidity with which drained wounds healed. The complications developing postoperatively in this group of 55 cases were few: three abscesses of the abdominal wall; one case of pyelitis; two fecal fistulas, both of which healed before discharge from the hospital, and four mild respiratory complications.

The average time before discharge in these cases was twenty days. The patients ranged in age from 4 months to 72 years.

For use in the operating room, the drug is placed in cork-stoppered test tubes in amounts of 2, 4, 6 and 8 Gm. It is then sterilized by dry heat for one-half hour at 120 C. The drug should not be autoclaved.

The powdered drug is placed in the peritoneal cavity just before the peritoneal layer is sutured or, in cases of abscess just before the drains are inserted. The amount used varied; in adults from 10 to 12 Gm. was the average used. The amount varied with the weight of the patient and the severity of the peritoneal infection. We have used as much as from 16 to 18 Gm. in severe conditions. Infants received from 2 to 4 Gm. One fourth the total amount is reserved for the layers of the abdominal wall during complete or partial closure of the wound.

Blood levels of the sulfanilamide reach a high level as soon as two hours after operation in cases in which drainage is not done. The peak of the blood level is reached in twelve hours and falls at the end of thirty-six hours. In cases in which drainage is done, the levels are usually slightly lower. The average blood level has been 7 mg. per hundred cubic centimeters of blood.

However, the blood level is of secondary importance, as the local level of the drug in the peritoneal exudate of from 200 to 300 mg. has a direct effect which cannot be produced in any other way. In 20 per cent of the cases the blood level was maintained postoperatively, the drug being given orally, rectally or by hypodermoclysis after the second day and continued for five or six days more.

Our results with the sulfanilamide at Roosevelt Hospital have been so consistently good in cases of severe peritoneal infection that we have not tried sulfathiazole powder, although we have used the latter elsewhere locally with good results.

R. STERLING MUELLER, M.D., New York.

## CHANGES IN PLASMA VOLUME

*To the Editor:*—In studying the behavior of the plasma volume during diuresis it is apparent that changes in the plasma volume will depend for their magnitude on the intensity of the diuresis in proportion to the volume of the plasma. To illustrate the superiority of the edematous dog to the edematous cardiac patient for experimental purposes in this respect, I give the following approximate average values taken from the recently published paper of Swigert and Fitz (THE JOURNAL, Nov. 23, 1940, p. 1786) and the papers of Bryan, Evans, Fulton and Stead (*Arch. Int. Med.* **55**:735 [May] 1935) and Evans and Gibson (*Am. J. Physiol.* **118**:251 [Feb.] 1937):

| | Plasma Volume | Urine Flow Before Salyrgan | Maximum Urine Flow After Salyrgan | Increase |
|---|---|---|---|---|
| Edematous cardiac patient | 3,000 cc. | 1.8 cc./min. | 5.8 cc./min. | 3.1 × |
| Edematous dog..... | 1,000 cc. | 0.6 cc./min. | 8.3 cc./min. | 14 × |

It may be inferred that trebling the flow of urine when the plasma volume is 3,000 cc. may place no burden on the equilibrium between the tissue fluids and the blood, whereas increasing the flow of urine fourteen fold and to a higher rate with a plasma volume of only 1,000 cc. would affect that equilibrium and produce demonstrable and consistent changes in the plasma volume.

The changes observed by Swigert and Fitz are not consistent, as they concede, and do not on the whole exceed the limits of biologic variation and experimental error, so that it does not seem reasonable to ascribe them to the diuresis induced by salyrgan.

WILLIAM A. EVANS JR., M.D., Detroit.

## AMPUTATIONS

*To the Editor:*—I have been following with interest the articles of the Council on Physical Therapy on "Amputations." Certain statements in Chapter III call for comment, since they would leave the inexperienced surgeon with a totally erroneous impression of the value of end bearing amputations. As we are again faced with the prospect of many amputations from war injuries it is of extreme importance that the experience of the past war be placed on record.

It cannot be too strongly emphasized that end bearing amputations (Syme and Stokes-Gritti) are greatly superior to all other forms of amputation in the lower extremity. The amount of weight which must be borne on a lower extremity stump is so great that only skin which is naturally adapted to weight bearing can be expected to stand the stress during a lifetime of usage. Amputations through the middle of the tibia in which the weight is taken on hairy skin against the oblique expanded end of the tibia are at a great physiologic disadvantage. This results in frequent complications due to hair follicle infections in the weight bearing area, painful indurations as well as the vascular disturbance known as "choked stump," which results in a boggy edematous end to the stump, which fissures and permits infection to enter. Of the below knee amputations through the tibia which were performed on Canadian soldiers of the last war a large proportion have been reamputated and converted into Stokes-Gritti amputations to the entire satisfaction of the patient, the surgeon and the limb maker.

Syme's amputation provides a stable, painless stump which never gives trouble because of the amount of weight it is called on to bear. The technic of the operation is not unduly difficult. The sole step of outstanding importance is to retain a good blood supply to the heel flap. It is better than Pirogoff's amputation, since it allows more space beneath the stump for the ankle joint mechanism of the artificial leg and because it avoids

the possibility of complications due to failure of the fragment of the calcaneus to unite by bone to the tibia. It is quite possible to make a very satisfactory artificial leg for Syme's amputation with an ankle joint mechanism in it, and excellent ones are being made by Canadian limb makers. It is true that it must be strong because of the leverage strains it must bear, and this means metal reinforcing, which means a moderately heavy limb. But even this feature has been overcome by the use of aluminum alloys, so that in the best types of limbs, such as the Dew limb, the weight does not exceed 3 pounds. The appearance means nothing in a male patient, for the limb is entirely concealed by his clothing. For women, by more elaborate craftsmanship, it can be made so inconspicuous as to be scarcely noticed. One of my Syme's amputations is in a young woman whose artificial limb is so much less noticeable than was her deformed extremity with its apparatus that her life has been completely transformed.

Functionally Syme's amputation is easily the best of all the amputations of the lower extremity. It permits weight bearing without any restrictions. The patient can be on his feet all day and work at heavy occupations. The gait is natural. The artificial limb is easy to fit and gives little trouble. Its only complications are due to misplacement of the weight bearing flap or undue looseness of the flap. These features, if necessary, can be corrected by secondary plastic operations. In my experience circulatory complications never occur in it. Compared with the midtibial amputation its advantages are so great that it should always be performed if possible. No midtibial amputation permits walking all day or the performance of heavy work, whereas this is common experience with Syme's amputation.

Stokes-Gritti's amputation above the knee has the same merits that Syme's amputation has below the knee. It permits full weight bearing on the end of the stump without any complications due to the weight bearing. The technic is slightly more difficult. It is essential that the patella be firmly fused to the femur without tilt or lateral displacement. If this is attained, a good functional stump is assured on which the patient can walk all day without disability from weight bearing. So useful is this amputation that it has been used to replace many below-knee stumps of poor weight bearing function. The loss of voluntary knee joint action has proved of less consequence than ability to stand and walk without periods of disablement due to damage to the skin from weight bearing.

It is a great mistake to condemn out of hand Syme and Stokes-Gritti amputations or to damn them with faint praise. Beyond doubt they are the best amputations of the lower extremity. It is a source of amazement to me that the British Ministry of Pensions in its recent brochure should condemn these weight bearing stumps. I can attribute its experience only to poor limb making. During the last war the Canadian government established its own limb factory, which was and still is an integral part of the soldier's hospital at Christie Street in Toronto. This resulted in direct control of the process of artificial limb making by the surgeons who dealt with amputations and with end bearing stumps and the artificial limbs that are fitted to them. There commonly is but little correlation between the surgeon and the artificial limb maker. It is a mistake, however, to say that satisfactory limbs cannot be made for Syme or Stokes-Gritti amputations. Some ingenuity may be needed but the problem is susceptible of satisfactory solution.

The problem of amputations is of such importance and is likely to be of so much more importance in the immediate future that I have found it impossible to refrain from comment on your important series of articles and especially on the subject of end bearing stumps in the lower extremity.

R. I. HARRIS, M.C., M.B., F.R.C.S.(C.), Toronto.
Associate Professor of Surgery, University
of Toronto Faculty of Medicine.

# Medical Examinations and Licensure

## COMING EXAMINATIONS

### BOARDS OF MEDICAL EXAMINERS
### BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Examinations of boards of medical examiners and boards of examiners in the basic sciences were published in THE JOURNAL, January 18, page 248.

### NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Parts I and II. Various centers, February 10-12. Exec. Sec., Mr. Everett S. Elwood, 225 S. 15th St., Philadelphia.

### EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Oral.* Part II, Cleveland, May 31-June 1. Final date for filing application is April 1. Sec., Dr. Paul M. Wood, 745 Fifth Ave., New York.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* April, in advance of the meeting of the American College of Physicians and June, in advance of the meeting of the American Medical Association. *Written.* Oct. 20. Final date for filing application is Sept. 1. Sec., Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Written.* Philadelphia, June 6-7. Sec., Dr. R. Glen Spurling, 404 Brown Bldg., Louisville, Ky.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Part II, Groups A and B, Cleveland, May 28-June 1. Final date for filing application is March 15. Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* Cleveland, May or June. Sec., Dr. John Green, 6830 Waterman Ave., St. Louis.

AMERICAN BOARD OF PATHOLOGY: *Oral and Written.* Cleveland, June 2-3. Final date for filing application is May 1. Sec., Dr. F. W. Hartman, Henry Ford Hospital, Detroit.

AMERICAN BOARD OF PEDIATRICS: Chicago, May 18, following the Region III meeting of the American Academy of Pediatrics. Boston, Oct. 12, immediately following the annual meeting of the American Academy of Pediatrics. Sec., Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: *Oral.* Washington, May 2-3. Final date for filing application is Feb. 22. Sec., Dr. Walter Freeman, 1028 Connecticut Ave., N.W., Washington, D. C.

AMERICAN BOARD OF RADIOLOGY. *Oral.* Cleveland, May 30-June 1. Final date for filing application is April 15. Sec., Dr. Byrl R. Kirklin, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: Part II. San Francisco, Feb. 3. *Written.* Part I. Various centers, April 2. Sec., Dr. J. Stewart Rodman, 225 South Fifteenth St., Philadelphia.

## South Dakota July Report

Dr. J. F. D. Cook, director, South Dakota Board of Medical Examiners, reports the written examination for medical licensure held at Rapid City, July 16-17, 1940. The examination covered 13 subjects and included 100 questions. An average of 75 per cent was required to pass. Three candidates were examined, all of whom passed. Five physicians were licensed to practice medicine by reciprocity and 1 physician so licensed by endorsement. The following schools were represented:

| School | PASSED | Year Grad. | Per Cent |
|---|---|---|---|
| Northwestern University Medical School | | (1940) | 86, 87.1 |
| University of Wisconsin Medical School | | (1939) | 85.9 |

| School | LICENSED BY RECIPROCITY | Year Grad. | Reciprocity with |
|---|---|---|---|
| Northwestern University Medical School | | (1937) | Michigan |
| State University of Iowa College of Medicine | | (1927) | Minnesota |
| Detroit College of Medicine and Surgery | | (1922) | Michigan |
| University of Minnesota Medical School | | (1938) | Minnesota |
| University of Pennsylvania School of Medicine | | (1936) | Minnesota |

| School | LICENSED BY ENDORSEMENT | Year Grad. | Endorsement of |
|---|---|---|---|
| Rush Medical College | | (1937) | N. B. M. Ex. |

## Hawaii July Report

Dr. James A. Morgan, secretary, Board of Medical Examiners, Territory of Hawaii, reports the oral and written examination for medical licensure held at Honolulu, July 8-11, 1940. The examination covered 10 subjects and included 80 questions. An average of 75 per cent was required to pass. Seven candidates were examined, all of whom passed. The following schools were represented:

| School | PASSED | Year Grad. | Per Cent |
|---|---|---|---|
| University of Colorado School of Medicine | | (1939) | 84.1 |
| Northwestern University Medical School | | (1939) | 79.1 |
| Tulane University of Louisiana School of Medicine | | (1937) | 79 |
| Harvard Medical School | | (1937) | 86.4 |

| | | |
|---|---|---|
| Columbia University College of Physicians and Surgeons | (1898) | 78.4 |
| Long Island College Hospital | (1914) | 81.5 |
| Ohio State University College of Medicine | (1938) | 81 |

Five physicians were licensed to practice medicine by endorsement from February 19 through August 26. The following schools were represented:

| School | LICENSED BY ENDORSEMENT | Year Grad. | Endorsement of |
|---|---|---|---|
| Northwestern University Medical School | | (1939) | N. B. M. Ex. |
| Indiana University School of Medicine | | (1936) | N. B. M. Ex. |
| University of Louisville School of Medicine | | (1936) | N. B. M. Ex. |
| Tulane Univ. of Louisiana School of Medicine | | (1936), (1938) | N. B. M. Ex. |

### Virginia June Report

Dr. J. W. Preston, secretary, Board of Medical Examiners of Virginia, reports the written examination for medical licensure held at Richmond, June 18-20, 1940. The examination covered 8 subjects and included 80 questions. An average of 75 per cent was required to pass. One hundred and thirty candidates were examined, 129 of whom passed and 1 failed. The following schools were represented:

| School | PASSED | Year Grad. | Per Cent |
|---|---|---|---|
| George Washington Univ. School of Med. | | (1939) 77, 87, (1940) | 84, 85 |
| Georgetown University School of Medicine | | (1940) | 83 |
| Howard Univ. College of Medicine | | (1939) 81, 83, (1940) | 80, 81, 88 |
| University of Minnesota Medical School | | (1940) | 80 |
| Johns Hopkins University School of Medicine | | (1940) | 84 |
| New York Medical College, Flower and Fifth Avenue Hospitals | | (1939) | 81 |
| Duke University School of Medicine | | (1938) | 77 |
| Jefferson Medical College of Philadelphia | | (1940) | 84 |
| Medical College of Virginia | | (1939) 88, (1940) 75, 78, 79, 80, 80, 81, 81, 81, 81, 81, 81, 82, 82, 82, 82, 82, 82, 83, 83, 83, 83, 83, 83, 83, 84, 84, 84, 84, 84, 85, 85, 85, 85, 85, 85, 85, 85, 86, 86, 86, 86, 87, 88, 88, 88, 89 | 85, |
| University of Virginia Department of Medicine | | (1938) (1940) 77, 77, 79, 79, 79, 79, 79, 80, 80, 80, 80, 81, 81, 81, 81, 81, 81, 81, 82, 82, 82, 82, 82, 82, 82, 82, 82, 82, 83, 83, 83, 83, 83, 83, 83, 83, 83, 84, 84, 84, 84, 84, 85, 85, 85, 85, 85, 85, 86, 86, 86, 86, 87, 88, 88 | 80, |
| University of Wisconsin Medical School | | (1938) | 84 |
| Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin | | (1931) | 75 |
| Vereinigten-Friedrichs-Universität Medizinische Fakultät, Halle Wittenberg | | (1920) | 84 |
| University of Edinburgh Faculty of Medicine | | (1934) | 81* |

| School | FAILED | Year Grad. | Number Failed |
|---|---|---|---|
| Université de Genève Faculté de Medicine | | (1936) | 1 |

Twenty-five physicians were licensed to practice medicine by reciprocity and 10 physicians so licensed by endorsement from February 27 through July 12. The following schools were represented:

| School | LICENSED BY RECIPROCITY | Year Grad. | Reciprocity with |
|---|---|---|---|
| College of Medical Evangelists | | (1932) | California |
| George Washington University School of Medicine | | (1927), (1932), (1934), (1938) | District of Colum., (1938) Penna. |
| Georgetown University School of Medicine | | (1933), (1937) | Dist. Colum. |
| Johns Hopkins University School of Medicine | | (1935), (1937) | Maryland |
| Washington University School of Medicine | | (1938) | Missouri |
| Cornell University Medical College | | (1936) | New York |
| University of Buffalo School of Medicine | | (1923) | New York |
| Ohio State University College of Medicine | | (1936) | Ohio |
| University of Cincinnati College of Medicine | | (1938) | Ohio |
| Jefferson Medical College of Philadelphia | | (1927) | Dist. Colum. |
| Meharry Medical College | | (1938), (1939) | Tennessee |
| University of Tennessee College of Medicine | | (1933), (1939) | Tennessee |
| University of Tennessee Medical Department | | (1901) | Montana |
| Vanderbilt University School of Medicine | | (1938) | Tennessee |
| University of Virginia Department of Medicine | | (1936) | Louisiana |
| Licentiate of the Royal College of Physicians of London and Member of the Royal College of Surgeons of England | | (1926) | Maryland |
| Université de Montpellier Faculté de Médicine | | (1932) | Penna. |

| School | LICENSED BY ENDORSEMENT | Year Grad. | Endorsement of |
|---|---|---|---|
| College of Medical Evangelists | | (1938) | N. B. M. Ex. |
| Georgetown University School of Medicine | | (1937) | N. B. M. Ex. |
| Northwestern University Medical School | | (1937) | U. S. Navy |
| Tufts College Medical School | | (1936) | N. B. M. Ex. |
| Albany Medical College | | (1938) | N. B. M. Ex. |
| Duke University School of Medicine | | (1937) | N. B. M. Ex. |
| Medical College of the State of South Carolina | | (1932) | N. B. M. Ex. |
| Meharry Medical College | | (1937) | N. B. M. Ex. |
| Medical College of Virginia | | (1937, 2) | N. B. M. Ex. |

* License has not been issued.

# *Bureau of Legal Medicine and Legislation*

## MEDICOLEGAL ABSTRACTS

**Medical Practice Acts: Injunction to Enjoin Disciplinary Proceedings by Licensing Agency Denied.**—The defendant Missouri State Board of Health, the state medical licensing agency, commenced disciplinary proceedings against the plaintiff physician, charging that he had been convicted of using the mails to defraud, had engaged in a prohibitive type of advertising relative to diseases of the sexual organs and had been guilty of other unprofessional and dishonorable conduct. In the manner prescribed by law the secretary of the board notified the plaintiff to appear at the hearing that was to be held before the board. Instead of appearing before that board and answering the charges made, the plaintiff filed a petition with the circuit court, St. Louis County, division 3, for an injunction to restrain the board from proceeding on its charges, alleging a subsequent pardon for the conviction and that the other charges did not constitute unprofessional conduct. The board demurred to the plaintiff's petition on the ground that the petition alleged insufficient facts to entitle the plaintiff to any relief, that the circuit court had no original jurisdiction in the premises and that under the laws of Missouri the state board of health had exclusive initial jurisdiction in revocation proceedings. From an order overruling its demurrer and granting the injunction, the defendant board appealed to the Supreme Court of Missouri, division 1.

The defendant contended that it was acting within its exclusive jurisdiction when it maintained proceedings to determine whether or not a license to practice medicine should be revoked and that the plaintiff was not entitled to an injunction restraining such proceedings because, if he felt aggrieved by the board's decision, he could have appealed to the circuit court by a writ of certiorari. The Supreme Court said that in general a court of equity will not interfere by injunction for the purpose of controlling the acts of public officers constituting inferior tribunals—such as supervisors, commissioners of highways and the like—on matters properly pertaining to their jurisdiction since the proper remedy was a review at law by writ of certiorari. The court therefore held that, since the defendant board was functioning lawfully within its exclusive initial jurisdiction, the plaintiff was not entitled to an injunction to restrain the board from proceedng to take disciplinary action against him. Judgment for the plaintiff was therefore reversed, and the preliminary restraining order was dissolved.—*Hughes v. State Board of Health, 137 S. W. (2d) 523 (Mo., 1940).*

**Malpractice: Alleged Failure Timely to Recognize and Advise Patient as to Nonunion of Fracture of Tibia.**—The plaintiff suffered on April 1 a spiral fracture of the tibia and a "rough" transverse fracture of the fibula, about opposite each other at the junction of the lower and middle third of those bones. He was hospitalized and the physician defendant reduced the fractures and applied a splint that day. A plaster cast was applied and roentgenograms were taken the following day. The patient was discharged from the hospital April 3 and was told to remain in bed for about thirty days, which he did, the defendant visiting him once in the interim. The patient returned to the defendant June 2. The physician, after taking another roentgenogram and opening the cast by splitting it lengthwise, informed the patient that the leg was "fine" and that a good callus was forming. The patient complained at that time that the leg was sore and painful. The physician "put part of the cast back" and advised the patient to use crutches. The patient returned late in June, complaining that his leg was still sore and painful, and the physician applied heat by an electric pad and again told the patient that the "break" was "coming fine" and that the callus was getting stronger. During early July the physician again saw the patient and took a third

roentgenogram. The leg at that time was "wobbly," it "sagged in the center" and was "turning out." The physician still advised that the leg was "coming along fine" and that a good callus was forming. The use of crutches was continued until late July when a cane was utilized. The plaintiff was never able to put his full weight on his left leg. On September 17 he again called at the physician's office, complaining that his leg was more pliable than ever and "that it was just like he had an extra joint between the knee and the ankle." The physician then made a fluoroscopic examination. About two weeks later the patient went to a clinic in a nearby town and was informed, apparently, that there was nonunion and that an operation would be necessary to effect a union. The patient told the defendant physician of this advice and on the defendant's suggestion Dr. Fortin, a "bone specialist" of Fargo, N. D., was put in charge of the case. The defendant accompanied the patient to Fargo the following day and a day later Dr. Fortin operated and found that the fibula had united but that there was nonunion of the tibia. He sawed off the ends of the fragments of the tibia and inserted between them a bone graft. What the end result was the published report of the case does not state. Subsequently the patient brought suit for malpractice against the defendant physician, and from a judgment in favor of the patient the physician appealed to the Supreme Court of North Dakota.

The complaint filed alleged that the physician breached his duty to his patient in that three months after assuming the care of the patient, and at times thereafter, he informed the patient that the leg was coming along all right and was in good condition and that the fracture had been properly reduced and was healing, and thereby deceived the patient into continuing under his care and treatment when the physician should have known, if proper regular and careful examination and treatment had been given, that the broken limb had not united and never had been properly reduced. The sole question before the Supreme Court was whether or not the evidence adduced at the trial was sufficient to justify a verdict and judgment for the patient. The only expert testimony, aside from that of the defendant, was that of Dr. Fortin who testified on behalf of the defendant, in effect, that the early treatment rendered by the defendant, including the application of the cast and instructions that the patient remain in bed for thirty days, was proper, that the cast should be permitted to remain on from six to eight weeks and that it then was proper to remove the cast to make an examination of the progress of healing. This witness examined the roentgenograms taken by the defendant on April 2, June 2 and July 5. With regard to the roentgenogram taken on June 2, he testified that it showed little callus; that it would be proper treatment at that time to immobilize the leg longer and instruct the patient to walk around with the aid of crutches, bearing some weight on the injured leg. The roentgenograms taken on July 5, he stated, indicated that nature had not thrown down callus in the process of healing the fractured tibia, although the fibula appeared to be united. At the time of the third roentgenogram, he further testified, "We know we have a delayed union or coming to a non union" and "There is no set course for that"; one might apply another cast or a splint, or one might operate and put in new bone and attempt to make nature throw down callus. He stated on cross examination, however, that by the time the third roentgenogram had been taken, that is, on July 5, three months after the injury, if no union had been effected, "the chances of getting bony union thereafter, except by operation, is wholly speculative . . . most of the time."

It is the duty of a physician, said the Supreme Court of North Dakota, citing 48 C. J. 1133, to act with the utmost good faith toward his patient, and if he knows that he cannot accomplish a cure or that the treatment adopted will probably be of no benefit, it is his duty to advise his patient of these facts, and if he fails to do so he is guilty of a breach of that duty. The evidence in the present case, continued the court, entirely justified the conclusion that the defendant deceived the patient both in July and in September, and at times in between, when he told him that the leg was coming along fine and that everything was all right. According to Dr. Fortin, the fracture was a very severe one and was located in an area where nonunion, if treated according to the methods which the defendant had utilized, was not at all unlikely, and he must have known in July and in September that there was no union and that union was unlikely. Nothwithstanding this, he did not inform the plaintiff of the seriousness of the situation. He in fact misrepresented the true situation to the patient. Nor did he inform his patient that another method of treatment, by operation, was accessible within easy reach. According to the evidence the defendant recognized at once, when informed of the patient's consultation with the clinic, that the situation required the services of a "bone specialist." The duty of a physician to his patient is measured by conditions as they exist and not by what they have been in the past or may be in the future. Today, with the rapid methods of transportation and easy means of communication, the horizon has been widened and the duty of a physician is not fulfilled merely by utilizing the means at hand in the particular village where he is practicing. So far as medical treatment is concerned, the borders of the locality and community have, in effect, been extended so as to include those centers readily accessible where appropriate treatment may be had which the local physician, because of limited facilities or training, is unable to give. The defendant not only failed to inform his patient as to the true condition of the broken bones as shown by the roentgenograms but made inaccurate and misleading statements concerning the same—statements that naturally would lead the patient to believe that the condition of his injured leg was wholly satisfactory and that the broken bones apparently were forming a proper and satisfactory union when the truth was that the roentgenogram showed only a "little callus present" and "a delayed union or coming to a non union." The defendant continued a treatment which, in the plaintiff's case at that time, was "conjectural and speculative," and he failed to inform the plaintiff that there was another method of treatment, namely surgery, available in a not distant city which was more likely to result in a union of the broken bones than the treatment that was being given. In the judgment of the court the evidence was sufficient to warrant the jury in finding that the defendant failed to perform the duty which he owed to the plaintiff and that, because of such failure, the plaintiff suffered detriment. If the defendant, on July 5, had informed the plaintiff of the true condition of the broken bone, as shown by the roentgenogram taken that day, and had further informed him as to the method of treatment that was most likely to effect a union of the broken bones, the plaintiff could and probably would have obtained such treatment some three months earlier than he did and thus have been spared at least three months of expense, pain and suffering.

Accordingly, the judgment in favor of the patient was affirmed. There was, however, a strong dissenting opinion by two justices who differed with the majority opinion as to the conclusions to be drawn from the testimony adduced.—*Tvedt v. Haugen, 294 N. W. 183 (N. D., 1940).*

## Society Proceedings

### COMING MEETINGS

Annual Congress on Medical Education and Licensure, Chicago, Feb. 17-18. Dr. W. D. Cutter, 535 North Dearborn St., Chicago, Secretary.

American Orthopsychiatric Association, New York, Feb. 20-22. Dr. Norvelle C. La Mar, 149 East 73d Street, New York, Secretary.

Central Surgical Association, Ann Arbor, Mich., Feb. 28-March 1. Dr. George M. Curtis, Ohio State University, Columbus, Ohio, Secretary.

Middle Section, American Laryngological, Rhinological and Otological Society, Chicago, Jan. 27. Dr. Walter H. Theobald, 307 North Michigan Blvd., Chicago, Chairman.

Mid-South Post Graduate Medical Assembly, Memphis, Tenn., Feb. 11-14. Dr. A. F. Cooper, Goodwyn Institute Bldg., Memphis, Tenn., Secretary.

Pacific Coast Surgical Association, Los Angeles, Feb. 19-22. Dr. H. Glenn Bell, University of California Hospital, San Francisco, Secretary.

Society of Surgeons of New Jersey, Newark, Jan. 29. Dr. Walter B. Mount, 21 Plymouth St., Montclair, Secretary.

Society of University Surgeons, St. Louis, Feb. 14-15. Dr. Frank Glenn, 525 East 68th St., New York, Secretary.

Western Section, American Laryngological, Rhinological and Otological Society, San Francisco, Feb. 1-2. Dr. Robert C. Martin, 384 Post St., San Francisco, Chairman.

# Current Medical Literature

## AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1930 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

### American Journal of Diseases of Children, Chicago

**60**:1245-1496 (Dec.) 1940

Behavior Disorders of Intellectual Origin Occurring in Childhood. M. W. Thorner and G. H. J. Pearson, Philadelphia.—p. 1245.

Possible Relation Between Electrolyte Balance and Bronchial Asthma. A. V. Stoesser and M. M. Cook, Minneapolis.—p. 1252.

*Prophylaxis and Treatment of Whooping Cough with Pertussis Antigen: Report of Results. C. L. Joslin and T. A. Christensen, Baltimore.—p. 1269.

Oral and Intravenous Dextrose Tolerance Tests in Cases of Acute (Catarrhal) Hepatitis. D. J. Pachman, Chicago.—p. 1277.

Relation of Dental Caries in Rural Children to Sex, Age and Environment. B. R. East and Hilda Kaiser, New York.—p. 1289.

*Results of Schick Test in Children One to Ten Years After Injections of Toxoid. B. Benjamin, G. Fleming, Montreal, Canada, and Mary A. Ross, Toronto, Canada.—p. 1304.

Olfactory Bulbs in Human Poliomyelitis. A. B. Sabin, Cincinnati.—p. 1313.

Roentgenologic Study of Anomalies of Hands in 100 Cases of Mongolism. H. W. Hefke, Milwaukee.—p. 1319.

Minimal Nitrogen Requirements of Children with Nephrotic Syndrome: Effect of Administration of Growth-Promoting Anterior Pituitary Extract. L. E. Farr, New York.—p. 1324.

Respiration in Newborn Infants. A. R. Bauer, Detroit.—p. 1342.

Meningitis Caused by Bacterium Coli Anaerogenes (Anaerogenic Coliform Organism): Report of Its Occurrence in a 3 Week Old Infant, with Temporary Cortical Insult and Recovery. S. Rauch and N. Krinsky, Brooklyn.—p. 1386.

**Pertussis Antigen for Prophylaxis and Treatment.**—Joslin and Christensen present results obtained with pertussis antigen (detoxified). The antigen had no effect with doses of 0.5, 0.8 and 1 cc. It was effective when the initial dose was increased to 1.5 cc. The authors had no standard on which to base the optimal dose, the most advantageous interval between doses or the total amount of antigen to be given. They divided their study into three parts: (1) the effect of the antigen on active pertussis, (2) its immunizing effect when administered as a routine to well children and (3) the influence on children exposed to pertussis but in whom sufficient time had not elapsed for the disease to develop. The antigen was given to 1,051 patients from 1 month to 10 years of age. The average duration of the attack was three and fifteen one-hundredths weeks. Twenty of the 1,051 patients treated showed no response to the antigen; they had severe pertussis. Reactions from the antigen were unusual. Occasionally a slight rise in temperature lasting twenty-four hours or a slight redness of the arm was observed. Three patients had an urticarial reaction. Thirteen patients who failed to return for further injections showed regression with progression of symptoms. In 6 of these patients there was a sluggish response to additional injections. There was a 94 per cent protection rate among children immunized with 6 cc. of antigen who were definitely exposed. In contrast, pertussis developed in 75 per cent of 200 children immunized with only 3 cc. of the antigen. The incidence of complications was reduced and the duration of the attack was shortened if the antigen was administered early. Results depended largely on the amount of antigen given per dose. Beyond a certain point additional antigen was of little value. Only 9 per cent of children receiving a second dose of 0.5 cc. responded, compared to 82 per cent of those patients receiving 1.5 cc. as a second dose. When a larger dose, 2 cc., was given the greatest response followed more equally the second and the third injections. The consistent increase of response corresponding to the increased amount of antigen given per dose is striking. The optimal interval between doses appears to be every second or third day; 82 per cent of the patients responded after four doses when the time interval between doses was three days, as compared to 63 per cent when the interval was four days. The duration of immunity varied from five months to two and a half years. A number of infants immunized during this study with a mixed vaccine and antigen exhibited no appreciable protection. Of 118 children immunized after exposure 90 escaped pertussis, while 28 contracted the disease.

**The Schick Test After Injections of Toxoid.**—Benjamin and his associates Schick tested children who were available for study after receiving diphtheria toxoid from one to ten years ago. Children who had received less than two injections of toxoid or those given diphtheria antitoxin were not included. The group consisted of 1,522 children; 39 had had only two doses of toxoid and no previous Schick test, 78 had two doses and a previous Schick test, 517 had three doses and no previous Schick test, 853 had three doses and a previous Schick test, 8 had a second test after the third dose of toxoid and 27 had a second test after a fourth dose of toxoid. Of 1,251 children Schick tested from one to eleven years after the third dose of toxoid a positive reaction was elicited in 14.9 per cent from five to eleven years later. This was twice as great as that observed in from four to five years after the third dose of toxoid. Up to the end of the fifth year, the advantage seems to be with those who had a previous test. For the later years the advantage is not maintained and favors those not having a previous test. A previous Schick test would probably not increase the number of positive reactors, although it is possible that its stimulus may wear off after about five years. In none of the children did the Schick reactions revert from negative to positive in less than two years after the third dose of toxoid; in 8.4 per cent they did revert from negative to positive in from two to ten years. Diphtheria toxoid given to infants 6 months old achieved immunization which, as gaged by the Schick test, is as lasting as that in older children. The authors suggest that all children who receive three injections of diphtheria toxoid in infancy be given either a Schick test at 5 years of age and, if the reaction is positive, a further subcutaneous injection of 1 cc. of toxoid or, if the test is omitted, the recommended dose of toxoid at this age.

### American Journal of Tropical Medicine, Baltimore

**20**:625-748 (Sept.) 1940

*Beriberi and Vitamin $B_1$ Deficiency. E. B. Vedder, Washington, D. C.—p. 625.

Dry Season Observations on African Mosquito Anopheles Gambiae in Brazil in 1938. R. C. Shannon and G. C. de Andrade, Rio de Janeiro, Brazil.—p. 641.

Effect of Change of Residence from Temperate to Tropical Climate on Basal Metabolism, Weight, Pulse Rate, Blood Pressure and Mouth Temperature of Twenty-One English and American Women. Eleanor D. Mason, Madras, India.—p. 669.

Plasma Potassium Level During Malaria Infection in Monkeys and Man. R. L. Zwemer, E. A. H. Sims and L. T. Coggeshall, New York.—p. 687.

Influence of Temperature on Plasmodium Vivax. W. K. Stratman-Thomas, Nashville, Tenn.—p. 703.

Immunologic Studies in Malaria, with Special Reference to Diagnosis of Malaria. W. K. Stratman-Thomas and Anna Dean Dulaney, Nashville, Tenn.—p. 717.

Natural Infection of Fetus with Leptospira Icterohaemorrhagiae in Wild Rat. T. G. Ward and T. B. Turner, Baltimore.—p. 727.

Intestinal Content Cultivation Medium: I. Methods of Preparation and Use and Data Obtained in Cultivation of Balantidium Coli from the Pig. E. C. Nelson, Lewiston, Maine.—p. 731.

**20**:749-898 (Nov.) 1940

Observations on Naturally and Artificially Induced Quartan Malaria. M. F. Boyd, Tallahassee, Fla.—p. 749.

Medicinal Prophylaxis of Amebiasis. C. F. Craig, San Antonio, Texas.—p. 799.

Incidence of Intestinal Protozoa Among Freshman Medical and Dental Students, with Especial Reference to Amebiasis. H. Tsuchiya and J. T. Jean, St. Louis.—p. 803.

Demonstration of Yellow Fever Antibodies in Animal Serums by Intracerebral Protection Test in Mice. J. C. Bugher, Bogota, Colombia, South America.—p. 809.

Study of Serums of Lepers in Quantitative Complement Fixation Tests for Syphilis and Tuberculosis. Elizabeth Maltaner, Albany, N. Y.—p. 843.

Residual Symptoms in Patients Following Recovery from Acute Infestation with Trichinosis. Z. Bercovitz, New York.—p. 849.

Life Cycle of Plasmodium Relictum Variety Matutinum. R. D. Manwell, Syracuse, N. Y.—p. 859.

Review of Literature on Exoerythrocytic Schizogony in Certain Malarial Parasites and Its Relation to Schizogonic Cycle in Plasmodium Elongatum. R. J. Porter and C. G. Huff, Chicago.—p. 869.

**Beriberi and Vitamin $B_1$ Deficiency.**—Vedder discusses the recent nutritional experiments on beriberi. A review of the work on vitamin $B_1$ suggests the possibility that degeneration of the nerves and the spinal cord may be produced by the deficiency of vitamins other than $B_1$. Under certain circumstances deprivation of vitamin A is capable of producing degenerative changes in the nervous system in at least puppies, rats and fowls. It may have a similar effect on human beings subsisting on a diet deficient in fat and vitamin A. Synthesization from the $B_2$ complex of a few of its six or more factors, namely nicotinic acid, riboflavin and $B_6$ and the recognition of pantothenic acid as an unknown hydroxyacid and beta alanine, has shown that only the latter cures chick dermatitis. The paralysis and the accompanying changes in the peripheral nerves can be prevented by riboflavin. But neither riboflavin, nicotinic acid nor vitamin $B_1$ prevents degeneration of the spinal cord. Pantothenic acid was also most effective in eliminating pathologic changes in the spinal cord. The conclusion is that riboflavin is necessary to the growing chick for the normal functioning and maintenance of the nervous system and pantothenic acid for maintaining the structures of the spinal cord intact. From these experiments it is seen that in later years, as experimental diets have become more refined and the nature of the $B_2$ complex has been better understood, the results become increasingly definite and specific. Deprivation of certain factors of the $B_2$ complex can undoubtedly produce demyelinization and degeneration of the axis cylinders of the peripheral nerves and of the spinal cord. There is no such definite experimentation on man. But applying these results to beriberi, it appears that persons living on an exclusive diet of polished rice, as many of the Oriental poor do, are as deficient in $B_2$ as they are in $B_1$, and that the extensive nerve degeneration from which they suffer may well be chiefly due to deficiencies of vitamin A and vitamin $B_2$. Those who in addition to the rice eat sufficient fish or meat do not suffer from $B_2$ deficiency. When deficiency of vitamin $B_1$, A and certain factors of the $B_2$ complex exists, profound degeneration of the entire nervous system (a combination of dry and wet beriberi, the mixed disease) is produced which cannot be promptly cured by pure vitamin $B_1$. A complete and adequate diet is the best treatment in these cases after preliminary treatment with thiamine.

## Archives of Dermatology and Syphilology, Chicago

**42**:993-1198 (Dec.) 1940

*Occupational Leukoderma. E. A. Oliver, Chicago; L. Schwartz and L. H. Warren, Washington, D. C.—p. 993.
*Ulcers of Legs in Sickle Cell Anemia. C. L. Cummer and C. G. LaRocco, Cleveland.—p. 1015.
Massive Destruction of Face. C. C. Dennie, T. R. Hamilton and H. F. Quinn, Kansas City, Kan.—p. 1040.
Acetylglycarsenobenzene in Treatment of Syphilis: Preliminary Report. W. H. Guy, B. A. Goldmann, G. P. Gannon and J. Slone, Pittsburgh.—p. 1046.
Acute Disseminated Lupus Erythematosus: Its Treatment with Sulfanilamide and Allied Products. U. J. Wile and H. H. Holman, Ann Arbor, Mich.—p. 1059.
Excretion of Bismuth in Urine of Patients Treated with Bismuth Ethylcamphorate. F. M. Thurmon and N. Benotti, Boston.—p. 1073.
Action of Iodine on Diseases of Skin as Influenced by Season and Weather. F. R. Schmidt, Chicago.—p. 1083.
*Cutis Verticis Gyrata and Acromegaly. E. P. Zeisler, Chicago, and L. M. Wieder, Milwaukee.—p. 1092.
Pityriasis-Rosea-like Dermatitis Following Gold Therapy: Report of Two Cases. U. J. Wile and C. J. Courville, Ann Arbor, Mich.—p. 1105.
Hereditary Edema of Legs (Milroy's Disease) Associated with Other Congenital Anomalies. W. A. Rosenberg, Chicago.—p. 1113.

**Occupational Leukoderma.**—Oliver and his associates report the occurrence of leukoderma in a tannery. The investigation was requested by an insurance company. The men affected claimed that the depigmentation was the result of wearing a certain type of rubber glove. At the first visit to the tannery, where 88 persons were employed, 20 of the affected men were examined. Only 48 of the 88 employees wore the rubber gloves, and of those wearing gloves 25 (52 per cent) had leukoderma. The involved areas corresponded with those covered by the heavy rubber gauntlet type of glove worn. The areas of leukoderma were milky white. Even in the most pronounced cases the palms and the dorsal aspects of the terminal phalanges of the fingers were unaffected. The skin showed no signs of acute or chronic dermatitis. The pigment about the hair follicles seemed the last to disappear and the first to reappear. After a thorough investigation, including patch tests of all the affected persons, an antioxidant added to the rubber for the purpose of improving its aging properties was found to be the cause. This antioxidant is known by the trade name agerite alba and is said to be the monobenzyl ether of hydroquinone. Patch tests made on unaffected volunteer subjects with the rubber and with the antioxidant in powder form, in a 75 per cent ointment and in a 20 per cent solution of alcohol, ether and collodion gave positive reactions in 2 cases. Tanning liquors played no part in the depigmentation. Investigation of all plants in which the particular gloves were worn by the workers showed the same type of leukoderma. The drug had no apparent effect on the general health of the persons, as examinations of the blood were within normal limits. The dopa reaction in biopsy specimens of the depigmented and repigmented skin was negative in the depigmented areas and positive in the repigmented ones. Repigmentation in many persons began soon after they ceased wearing the incriminating gloves. The authors believe that the monobenzyl ether of hydroquinone antioxidant has a physiologic action on the skin that other antioxidants do not have. At present they do not know how this drug acts on the cutaneous pigment. It apparently prevents the formation of melanin, either by action on the cells which form melanin or by action on one or more of the intermediate products in the formation of melanin from the amino acid tyrosine. The latter theory seems the more likely, as the cells do not appear damaged.

**Ulcers of Legs in Sickle Cell Anemia.**—Cummer and LaRocco report 5 cases of ulcers on the legs accompanying sickle cell anemia observed at St. Vincent Charity Hospital. They list the following available facts in an attempt to explain their causation: 1. Such ulcers occur in a definite proportion of persons suffering from sickle cell anemia and in a lower proportion of those with the sickle cell trait only. 2. They must be rare in pernicious anemia and chlorosis but they are encountered in congenital hemolytic jaundice. Their occurrence may be more frequent than is recognized now. 3. Murphy has advanced the opinion that sickle cell anemia may be the typical manifestation of familial hemolytic anemia in the Negro in whom, possibly because of some difference in the structure of the erythrocytes, sickle cells appear instead of spherical erythrocytes. 4. The ulcers in sickle cell anemia seem to have been induced, or at least preceded, by infection or trauma. Their size and duration are out of all proportion to the infection or trauma. 5. They show no specific distinguishing histologic features from other chronic ulcers. The authors advance the following theories: 1. The ulcers have been produced by injury or infection and have become chronic because of associated malnutrition or the lowered vitality of anemic tissue. 2. Against this is the apparent lack of evidence that similar lesions occur in other severe anemias, notably chlorosis, which affects adolescent girls of the same age as those with sickle cell anemia in whom ulcers of the legs develop most frequently. That they are coincidental is not plausible, as they occur more often in sickle cell anemia than in the sickle cell trait. 3. Capillary blocking as a cause would not explain similar ulcers in chronic hemolytic jaundice, in which thromboses are not a part of the process and the erythrocytes are not elongated but spherocytic. The ulcers are usually punched out, may be single or multiple and unilateral or bilateral and usually occur at the ankle. Their course is extremely chronic. Simple local applications seem the most effective treatment. The microscopic picture is that of chronic granulomatous ulcers. Anemia should be considered as a possible explanation for old chronic ulcers on the legs, especially in younger persons.

**Cutis Verticis Gyrata and Acromegaly.**—Zeisler and Wieder believe from study of the literature and consideration of their own 2 cases that cutis verticis gyrata may be added to other clinical signs pointing to pituitary disease. It may be the only external sign and therefore be overlooked. Such was the case in 1 of their patients. Although the condition was observed in only a few instances of acromegaly described in the literature, it is probable that more may have had this early sign of oncoming pituitary disease than were recognized. Because of this, the authors wish to reemphasize the need for careful study, with the inclusion of routine roentgen examination of the skull and

extremities of this group of cases. The finding of a sella normal in size on roentgen study does not necessarily negate the diagnosis of associated cutis verticis gyrata with acromegaly. This was illustrated by Sisson's case, which, although one of frank acromegaly, showed a sella of apparently normal size. Dermatologists may be the first to see these patients, and their prompt recognition of its significance may bring about the detection of a serious underlying disease. The authors believe, to the best of their knowledge, that they are citing the third and fourth instances of cutis verticis gyrata associated with pituitary disease to be reported in the American literature. The first was reported by Sisson and the second by Cushing and Davidoff, who termed the disorder "bulldog scalp." Occasionally brain surgeons have accidentally encountered this anomaly in the course of operations on the pituitary.

## Journal of Immunology, Baltimore

**39**:369-440 (Nov.) 1940

Effect of Dilution on Reaction Between Pneumococcus and Its Specific Antibody. M. C. Morris, St. Louis.—p. 369.
Role of Diffusion in Pneumococcus-Antipneumococcus Reaction. A. D. Hershey, St. Louis.—p. 383.
Serology of Pneumococcus Group. F. Kauffmann, E. Mørch and K. Schmith, Copenhagen, Denmark.—p. 397.
*Studies on Immunization of Adults with Diphtheria Toxoid. C. P. Bunch, R. C. Morrow Jr., J. R. Timmons and D. T. Smith, Durham, N. C.—p. 427.

**Immunization of Adults with Diphtheria Toxoid.**—After studying the various procedures recommended for the immunization of adults with diphtheria toxoid and from their observations on 90 Schick positive subjects, Bunch and his associates found the intracutaneous injection of minute doses of toxoid to be an easy regimen. Twenty-six of 27 such subjects became Schick negative, leaving only 1 to undergo a series of graded subcutaneous doses. The plan they adopted for the whole group is as follows: A Schick test is made on the persons to be immunized and a Moloney test on the Schick positive individuals. The M— and M+ reactors are given as a routine 2 cc. of undiluted toxoid in 1 cc. subcutaneous doses at intervals of one month. The M++ and M+++ reactors are given three 0.1 cc. intracutaneous injections of toxoid used for the Moloney test (a 1:100 dilution of toxoid) at weekly intervals. Schick tests are performed from three to six months after the last injection. If any M++ or M+++ subjects remain Schick positive, they are inoculated with a series of graded subcutaneous injections.

## Laryngoscope, St. Louis

**50**:1025-1106 (Nov.) 1940

Review of Available Literature on Pharynx and Pharyngeal Surgery for 1939. F. E. LeJeune and P. J. Bayon, New Orleans.—p. 1025.
Information Please: Regarding Hearing Aids and Audiometers. F. T. Hill, Waterville, Maine.—p. 1054.
Polypoid Tumors of Esophagus: Report of Two Cases. J. J. Mahoney, New York.—p. 1086.
Some Problems in Nasal Plastic Surgery. C. R. Straatsma, New York.—p. 1092.
Are Unwise Efforts Being Made to Connect the Avenue of Infection in Poliomyelitis to Trauma Following Adenoid and Tonsil Operations? Does an Unknown Port of Entry, Uncertain Incubation Period and Debatable Strain of So-Called Filtrable Virus Warrant Any Such Assumption? H. G. Langworthy, Dubuque, Iowa.—p. 1100.

## New England Journal of Medicine, Boston

**223**:877-916 (Nov. 28) 1940

*Sulfathiazole Therapy of Staphylococcus Aureus Bacteremia. C. H. Rammelkamp and C. S. Keefer, Boston.—p. 877.
Tularemia: Report of Case Contracted on Cape Cod. R. E. Moss and L. R. Evans, Boston.—p. 885.
Pneumococcic Cross Infections in the Home and Hospital. H. A. Holle and J. G. M. Bullowa, New York.—p. 887.
Hodgkin's Disease: Report of Case with Unusual Longevity and Invasion of Heart and Pericardium. M. Ritvo, Boston.—p. 891.
Multiple Pulmonary Thrombi Associated with Cyanosis and Right-Sided Cardiac Hypertrophy: Report of Case. V. G. Balboni, Boston.—p. 896.
Treatment of Juvenile Diabetes Mellitus. A. M. Butler, Boston.—p. 900.

**Sulfathiazole for Staphylococcus Aureus Bacteremia.**—Rammelkamp and Keefer cite 7 cases of Staphylococcus aureus bacteremia in which sulfathiazole was administered. In addition they studied the bactericidal properties of the blood obtained from 3 patients and from 5 normal persons following the oral administration of sulfathiazole. The number of cases treated is too small to judge the efficacy of the therapy. Age and the accessibility of metastatic abscesses to surgical drainage are important factors influencing the course of the disease. Prognosis is considered grave after 40; 4 of the patients, 1 of whom recovered, were 40 or more years of age. In the 3 patients who recovered the abscess was drained. In 1 of these there was, in addition to the abscess in the right thigh, an empyema that became sterile during sulfathiazole therapy. Surgical drainage of localized staphylococcic abscesses seems essential to recovery in most cases. The blood studies show that sulfathiazole when given by mouth to normal persons and to patients with bacteremia increases the bactericidal and bacteriostatic action of the blood against pathogenic staphylococci. Therefore the authors believe that sulfathiazole either sterilized the blood stream or lowered the number of organisms in the circulating blood. This may be valuable in preventing metastatic abscesses during invasion of the blood stream. The development of these metastatic abscesses (in 82 per cent of cases) which cannot be drained determines the fatal outcome in the majority of cases. The level of sulfathiazole in the blood stream should be between 3 and 5 mg. per hundred cubic centimeters. If the patient is anemic, blood transfusions should be given until the blood count is normal. Immediate drainage of all localized abscesses is of the utmost importance. A sustained fever or continuously positive blood cultures are usually signs of further abscess formation, and they should be searched for thoroughly. Toxic manifestations should be watched for and daily blood counts and urine analyses should be made. In the cases reported no serious toxic manifestations were observed.

## New York State Journal of Medicine, New York

**40**:1693-1760 (Dec. 1) 1940

Development of Voluntary Health Insurance in the United States. D. K. Freedman and Elinor B. Harvey, New York.—p. 1699.
Hazards of Pregnancy and Labor in the "Grande Multipara." N. J. Eastman, Baltimore.—p. 1708.
Certain Eye Factors in Prevention of Motor Vehicle Accidents. C. Berens, New York.—p. 1713.
The Elmira Tumor Clinic: Survey of Work After Six Years of Its Existence. M. Dreyfuss, Elmira.—p. 1725.
Emphysema: Dominant Finding in Acute Respiratory Infection: Preliminary Report of Possibly New Clinical Picture. Margaret R. Reynolds, Jackson Heights.—p. 1729.

## Oklahoma State Medical Assn. Jour., Oklahoma City

**33**:1-58 (Nov.) 1940

Hypertension. C. A. Traverse, Alva.—p. 1.
Pellagra. V. H. Musick, Oklahoma City.—p. 4.
Value of Metrazol Convulsive Shock in Psychiatric Therapy. G. W. Robinson Jr., Kansas City, Mo.—p. 8.
Sinus Disease in Children. C. H. Hall, Oklahoma City.—p. 12.
Modernizing Medical Public Relations. H. T. Sethman, Denver.—p. 16.

## Public Health Reports, Washington, D. C.

**55**:2195-2250 (Nov. 29) 1940

Tumor Clinic of the Baltimore Marine Hospital. E. R. Bryan.—p. 2195.
National Health Survey: Receipt of Medical Services in Different Urban Population Groups. R. H. Britten.—p. 2199.
Colorado Tick Fever. N. H. Topping, J. S. Cullyford and G. E. Davis.—p. 2224.

## Radiology, Syracuse, N. Y.

**35**:521-650 (Nov.) 1940. **Partial Index**

Roentgen Ray Examination with Miller-Abbott Tube. R. Golden, Octa C. Leigh and P. C. Swenson, New York.—p. 521.
Roentgenologic Findings in Acute Obstruction of Colon, with Particular Reference to Acute Volvulus of Sigmoid. L. G. Rigler and O. Lipschultz, Minneapolis.—p. 534.
Behavior of Small Intestine During Urinary Tract Irritation. K. D. A. Allen and J. H. Jamison, Denver.—p. 544.
Role of Intestinal Intubation in Diagnosis and Localization of Intestinal Obstruction. J. E. Lofstrom and R. J. Noer, Detroit.—p. 546.
Treatment of Cancer of Lip and Mouth. G. E. Pfahler, Philadelphia.—p. 598.
Use of Zinc Peroxide in Infected Tumors and Radiation Necrosis: Report of Cases, with Technic. D. A. Sunderland and J. S. Binkley, New York.—p. 606.
Roentgen Diagnosis of Cholecystocolic Fistula. C. A. Stevenson and M. W. Sherwood, Temple, Texas.—p. 616.
Familial Brachyphalangy. M. D. Sachs, Portland, Ore.—p. 622.

## Rhode Island Medical Journal, Providence

**23**:205-222 (Dec.) 1940

X-Ray Study as Aid to Diagnosis of Placenta Praevia. P. Appleton, Providence.—p. 205.
Report of Bagging Cases at Providence Lying-In Hospital: Jan. 1, 1926 to Dec. 31, 1938, Period of Thirteen Years. C. S. Houston, Providence.—p. 207.
Providence Lying-In Hospital Toxemia Clinic: Preliminary Report. W. S. Jones, Providence.—p. 209.

## Surgery, Gynecology and Obstetrics, Chicago

**71**:697-830 (Dec.) 1940

*Venography, Clinical Study. J. Dougherty and J. Homans, Boston.—p. 697.
Differentiation of Benign from Malignant Polypoid Bronchial Tumors. H. Brunn and A. Goldman, San Francisco.—p. 703.
*Factors in Recurrence of Varicosities Following Treatment. L. K. Stalker and W. W. Heyerdale, Rochester, Minn.—p. 723.
Studies in Malignant Testis Tumors: III. Incidence and Nature of Tumors in Ectopic Testes. J. B. Gilbert, Schenectady, N. Y., and J. B. Hamilton, New Haven, Conn.—p. 731.
Estrogen Therapy of the Climacteric: Analysis of Seventy-Seven Personal Cases. E. C. Smith, New Orleans.—p. 744.
*Benign and Malignant Cystic Tumors of Appendix. R. Woodruff and J. R. McDonald, Rochester, Minn.—p. 750.
Adenosis of Vagina and Its Relation to Primary Adenocarcinoma of Vagina. A. Plaut and M. L. Dreyfuss, New York.—p. 756.
Use of Asparagin Bacteriophage in Treatment of Acute Hematogenic Osteomyelitis. P. S. MacNeal, Ann Arbor, Mich.—p. 766.
Correlation Between Clinical and Experimental Findings in Cases Showing Invasion of Blood Stream by Staphylococci. B. Kleiger and J. E. Blair, New York.—p. 770.
Preparation and Preservation of Sterile Citrated Blood Plasma by Ampule Tube Method. R. T. Crowley, Detroit.—p. 777.
Webbed Fingers. D. W. MacCollum, Boston.—p. 782.
Pedicle Tube Graft in Surgical Treatment of Hypospadias in the Male, with New Method of Closing Small Urethral Fistulas. D. M. Davis, Philadelphia.—p. 790.
Method for Prevention of Spread of Osteomyelitis of Bones of Skull. W. P. Van Wagenen, Rochester, N. Y.—p. 797.
Recurrent Inguinal Hernia: Importance of Artificial Fibroplastic Proliferative Phase in Hernia Repair. C. L. Wilmoth, Pittsburgh.—p. 802.
Device for Making Accurate Roentgenograms of Neck of Femur During Reduction. H. McKenna, Chicago.—p. 808.
Surgical Treatment of Ectopic Testes. O. S. Lowsley, New York, and H. C. Curtis, Hamilton, Bermuda.—p. 811.
Breech Delivery. W. D. Hawker and S. D. Soule, St. Louis.—p. 819.

**Venography.**—Dougherty and Homans made venograms in 15 cases, 6 of which were normal and 9 abnormal. There was no reaction to the diodrast (an organic iodide). In the normal cases the solution passed freely into both the deep and the superficial circulation. In 1 or 2 of the earlier cases the superficial circulation filled more readily than the deep, probably because the injection was made directly into one of the small tributaries of the greater, rather than the lesser, saphenous system. In practically every abnormal case there was rather pronounced resistance to the rate of injection. A greater force was required to cause the solution to enter the deep circulation and a longer time was necessary to complete the injection. This may have been due to venospasm or mechanical blocking of the circulation. In a few instances the roentgen results suggested spasm, but in others it seemed that the irregular outline of a thrombus could be seen or that the opaque substance failed to enter the vessel because it was blocked. In several instances light compression by rubber tubing, usually above the knee, had little effect on causing the diodrast-laden blood to enter the deep circulation. The direction of flow evidently depended on the existence of some intrinsic factor such as thrombosis or spasm of the wall of the vessel and not on limited expansion by periphlebitis or generalized edema of the tissues of the extremity. The authors limited their investigation to the lower extremities and the adjacent portions of the body and were principally concerned with thrombosis. They cite 2 of their cases; the first was one of acute femoro-iliac thrombophlebitis accompanied by arterial spasm and the second a case of traumatic femoro-iliac thrombosis, subsequently canalized and complicated by recurrent small embolisms.

**Recurrence of Varicosities Following Treatment.**—Stalker and Heyerdale state that more than 50 per cent of the patients with varicosities of the lower extremities treated at the Mayo Clinic have associated incompetent great saphenous veins. A high incidence of recurrence has been observed when simple injection treatment was carried out. This has been eliminated by division and ligation of the great saphenous vein together with the injection of sclerosing solutions into the portion of vein distal to the ligation at the saphenofemoral junction, together with separate division and ligation of its uppermost tributaries. Recurrence has been reported even after this treatment. In the authors' experience the incidence of recurrence in this group has been exceedingly small. For the most part these recurrences can be prevented if the many variations in the anatomy of the great saphenous vein and its tributaries at the fossa ovalis are recognized and adequately treated at operation. After careful clinical study and examination at the first and second operations they believe that the recurrences have been due to technical mismanagement of the primary operation. Probably the tendency toward varicosities cannot be eliminated entirely. Unless the variations in the anatomic relationships of the great saphenous vein, its tributaries and surrounding structures around the fossa ovalis are recognized, some condition which may result either in a complete or a partial operative failure with resulting persistence or recurrence of an incompetent great saphenous system may be overlooked. The continuity of the veins of the lower extremity with those of the abdomen explains canalization of a thrombosed vein or dilatation of collateral vessels that act as shunts around the site of ligation of the saphenofemoral junction. Through these shunts hydrostatic pressure, augmented by spasmodically variable intra-abdominal pressure, is brought to bear on the veins distal to the ligation. Therefore it is necessary to divide and ligate separately, at the proper site, not only the great saphenous vein but also its tributaries. The relationship of these tributaries to the parent vein is not always constant, and a sufficiently wide exposure is necessary for their proper identification. Extreme care must be exercised, as a dilated superficial femoral vein may be mistaken for the great saphenous vein. The failure to excise a segment of vein may lead to recurrence owing to canalization. The injection of a sclerosing solution into the portions of divided veins distal to the ligation is of definite advantage.

**Benign and Malignant Cystic Tumors of Appendix.**—Woodruff and McDonald point out that from January 1914 to July 1938 approximately 43,000 appendectomies were performed at the Mayo Clinic. Examination of the appendixes disclosed 136 to have a so-called mucocele and 10 a grade 1 adenocarcinoma in a cyst. This incidence (0.3 per cent) agrees favorably with reports in the literature. The youngest patient among the 136 with simple mucoceles was 4 and the oldest 70 years of age. This group was studied individually. The authors concluded that mucoceles of the appendix are the result of stricture of the lumen, which usually is caused by inflammation. The benign nature of the growths was established. For the cystocarcinomas the hypothesis is presented that they are the result of malignant change in the wall of the benign mucocele. Simple mucoceles seem to have little clinical importance. At times a benign cyst of the appendix may be the cause of vague symptoms, but on the whole it has little significance. Cystocarcinomas of the appendix rarely reach clinical stages, but potentially they may rupture and be the cause of pseudomyxoma peritonei with a lethal outcome. The authors believe that the opinion of many other workers that pseudomyxoma peritonei of appendical origin is less malignant than that originating in the ovary is erroneous and is due to the fact that many of the reported cases were not really malignant but due to the escaping of the innocuous contents of benign cysts into the abdominal cavity. On the other hand, the fatal cases probably all originated in a carcinomatous cystadenoma of the appendix.

## Wisconsin Medical Journal, Madison

**39**:897-996 (Nov.) 1940

The Doctor and Democracy. E. J. Carey, Milwaukee.—p. 915.
What Confronts America and the Western Hemisphere Today. R. M. Immell, Madison.—p. 924.
Industrial Health as It Relates to National Preparedness. S. J. Seeger, Milwaukee.—p. 929.
Perinephric Abscess: Review of Twenty-One Cases, with Special Reference to Anaerobic Infection. B. B. Madison, Springfield, Ill.—p. 932.
Cardiovascular System as Related to Surgical Risk. W. T. Casper, Milwaukee.—p. 935.
New Use for an Old Idea. R. H. Gray, La Crosse.—p. 938.
Maternal Care and Maternal Mortality, with Special Reference to Progress in Wisconsin. E. F. Daily, Washington, D. C.—p. 940.
Wisconsin Marches On. Amy Louise Hunter, Madison.—p. 944.

## FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

### British Journal of Dermatology and Syphilis, London

**52**:321-352 (Nov.) 1940

Treatment of Pruritus Vulvae, Leukoplakia and Kraurosis. Agnes Savill.—p. 321.
Two Severe Dermatoses Treated with Sulfonamide Preparation. H. MacCormac.—p. 339.

### Lancet, London

**2**:537-576 (Nov. 2) 1940

The Moynihan Tradition. G. Gordon-Taylor.—p. 537.
Reality of Partial Deficiencies. L. J. Harris.—p. 539.
Estimation of Blood Volume in Plasma Transfusion. S. R. M. Bushby, A. Kekwick and L. E. H. Whitby.—p. 540.
Galactose Tolerance Test in Experimental Liver Necrosis. E. J. King, C. V. Harrison and G. E. Delory.—p. 541.
*Intravenous Galactose Tolerance Test. E. J. King and R. S. Aitken.—p. 543.
*Effect of Calcium on Diuresis in Cardiac Decompensation. N. Morris and A. S. Rogen.—p. 545.
Splints for Fingers and Thumb. W. I. de C. Wheeler.—p. 546.
Polyradiculoneuritis (Guillain-Barré's Syndrome) in East Anglia. H. S. Barber.—p. 548.
Morbidity and Death Rates in the Great Towns. P. Stocks.—p. 550.

**Intravenous Galactose Tolerance Test.**—According to King and Aitken the oral galactose tolerance test introduced by Bauer in 1906 is only a rough test of liver function. The rate of absorption of galactose is greater than that of any other sugar in the rat. This led to the belief that galactose is an ideal substance for use in tolerance tests. But its rate of absorption in man is variable and, after 40 Gm. has been taken by mouth, the blood galactose may be anything from a few milligrams to 60 mg. per hundred cubic centimeters. This great variation in the peak of the blood galactose curve suggested that a more satisfactory procedure would be to give the sugar intravenously to insure flooding of the system with galactose at the beginning of the test. The rate at which galactose disappeared from the blood should then furnish some measure of the glycogenic function of the liver, which is the principal tissue concerned with its conversion into glycogen. Intravenous galactose tolerance tests have been employed for some years. In these tests a relatively small dose of galactose (from 8 to 10 Gm. in a 40 per cent solution) was administered and the total blood sugar estimated at short intervals for from one half to one hour. King, Harrison and Delory tested the hepatic function of animals with artificially produced liver damage after the administration of large amounts of sugar. This work led to a study of liver function tests and to the development of an intravenous galactose test for application in man. The authors describe the technic and results of a galactose tolerance test of hepatic dysfunction in which 50 cc. of a 50 per cent solution of galactose is injected intravenously and the blood galactose is determined at half hour intervals thereafter. This modification of the galactose tolerance test is free from theoretical objections, and the results given show that in nearly all cases it distinguishes clearly between jaundice due to liver cell damage and jaundice due to gross obstruction of the biliary tract without liver cell damage. That is its practical value; it is not suggested that it will detect minor grades of liver damage in patients who are not jaundiced.

**Calcium for Diuresis in Cardiac Decompensation.**—Morris and Rogen point out that in many patients with cardiac failure one of the objects of treatment is to get rid of edema fluid and that calcium salts have been used to aid the diuretic action. Most of the work previously undertaken on the diuretic action of calcium has been done with the chloride, which probably owes its efficiency to its acid-producing effect. In the present investigation it was desired to determine the effect of calcium uninfluenced by tendency to acidosis. Accordingly calcium gluconate was used; in later cases solution of parathyroid was employed to raise the concentration of calcium in the serum. Calcium gluconate was administered intravenously to 10 patients with cardiac edema. It had little immediate effect on the urinary output. In 6 of 7 patients who had previously been receiving digitalis the diuretic effect of this drug was increased when given after a course of injections of calcium gluconate. In 9 of 10 patients with cardiac edema, injections of solution of parathyroid enhanced the diuretic action of salyrgan and digitalis.

**2**:577-610 (Nov. 9) 1940

Virus Diseases Acquired from Animals. S. P. Bedson.—p. 577.
Exophthalmic Ophthalmoplegia. H. G. McGregor.—p. 579.
*Combined Immunization with Tetanus Toxoid and T. A. B. I. H. Maclean and L. B. Holt.—p. 581.
Traumatic Rupture of Infrapatellar Tendon: Results of Repair by Fascial Suture. W. A. Cochrane.—p. 583.
Hemorrhagic Thrombocythemia. J. Reid.—p. 584.
*Effect of Smoke on Bacteria in Air. C. C. Twort and A. H. Baker.—p. 587.
Fatal Pellagra in an English Schoolgirl. R. E. H. Simpson.—p. 589.

**Combined Tetanus Toxoid and T. A. B. Immunization.**—Maclean and Holt point out that twenty-four years ago simple typhoid vaccine was combined with paratyphoid vaccine in the formula which is generally known as T. A. B. Immunization with this vaccine is accomplished by two doses administered at an interval of from seven to ten days. Ramon and Zoeller were the first to immunize large numbers of human subjects with tetanus toxoid, and various systems of dosage of tetanus toxoid were tried. Ramon and Zoeller then demonstrated that if tetanus toxoid is administered with T. A. B. vaccine the antitoxic response to the toxoid is greater than if it is given alone. The method used by Ramon is three doses of the vaccine-toxoid mixture with intervals of two or three weeks between doses. Maclean and Holt wished to immunize men simultaneously against tetanus and the enteric fevers with the minimum number of inoculations and found that the simplest effective method was to give two doses of the combined antigens (T. A. B. T.) at an interval of four weeks. The response to the antigens of the T. A. B. vaccine was as good as if these were administered at the usual short interval of one week. The amount of tetanus antitoxin in the serum of the immunized man was more than five times as great as it was in those who had two doses of tetanus toxoid alone at intervals of four or six weeks. Every subject tested who had been immunized with two doses of T. A. B. T. at a four weeks interval had an antitoxic titer of more than 1 unit of antitoxin per cubic centimeter in his serum, which is much higher than that which is accepted as an immunizing level against tetanus. In 50 per cent the antitoxic titer rose to 5 units or more per cubic centimeter, which is many times higher than would be reached by the usual prophylactic dose of tetanus antitoxin. The reaction to the combined antigens (T. A. B. T.) was no greater than to the T. A. B. vaccine alone.

**Effect of Smoke on Bacteria in the Air.**—In the course of investigations on germicidal aerosols, Twort and Baker examined the possibility of interference with the activity of the germicide mists by different kinds of smoke, more especially tobacco smoke. They found that exhaled tobacco smoke interfered with the effect of a phenolic germicidal aerosol in a concentration of 1 Gm. in 680 cubic meters of air on a suspension of Escherichia coli. Smokes produced by six smoldering organic substances were lethal to four bacterial suspensions tested, the flora of a normal saliva being much more sensitive than broth emulsions of three laboratory cultures. Cardboard and incense were the most satisfactory materials used, there being evidence of some lethal effect of the incense smoke in a concentration of 1 Gm. in 3,000 cubic meters of air after half an hour's contact with the atomized saliva. In calculating concentrations of smoke no account has been taken of unburned carbon, ash or material passing into the air as vapor (presumed inactive as germicidal aerosols). Estimations, by aspiration, of the actual quantity of smoke present in the air under test resulted in the recovery of only about 25 mg. for every 100 mg. of crude incense burned. Incense smoke, under the experimental conditions, persists in the particulate form, liquid or solid, for at least half an hour. Magnesium oxide and ammonium chloride smokes in a concentration of 1 Gm. in 10 cubic meters of air had no apparent lethal effect on an atomized broth emulsion of a laboratory culture. Infection of the respiratory apparatus of mice with a bacterial suspension of Salmonella enteritidis ("Liverpool virus" strain) was mostly prevented by decontamination of the air with cardboard and incense smokes in a concentration lower than 1 Gm. in 30 cubic meters of air.

## Presse Médicale, Paris

**48**:681-688 (Aug. 28-31) 1940

*Thymectomy for General Asthenia with Marked Retardation of Growth and Puerility: Case. R. Leriche and A. Jung.—p. 681.
Experimental Studies of Pulmonary Embolus. G. Pascalis.—p. 682.

**Thymectomy for Asthenia and Growth Retardation.**—Leriche and Jung report the case of a girl aged 17 years but presenting the appearance of a child from three to four years younger, with a history of chronic fatigability and progressive physical and mental debility, in whom ablation of the thymus effected a veritable transformation. The patient had undergone an appendectomy four years earlier, making an uneventful recovery, and two years later had had an attack of measles, which was of short duration but required three months for recovery. An assumed endocrine insufficiency had been vainly combated with appropriate medication. At the time of hospitalization, the patient weighed 88 pounds (40 Kg.) and complained of being always cold and tired. Any serious effort prostrated her and necessitated excessive sleep. Clinical observations and numerous roentgen tests disclosed no pathologic condition of the organs and revealed no thymus. The only diagnostic indications were the poor physical appearance, extreme fatigability and a dry skin. Guided by a similar previous experience, the authors had recourse to thymectomy. A quite well developed, very active thymus was found, forming a compact pinkish white mass 11 cm. in length and weighing 25 Gm., attached to the posterior sternum. Microscopic examination showed the presence of numerous Hassall's corpuscles without pathologic characteristics. The patient was discharged at the end of a week and already at that time showed a remarkable change. Seen two months later, she could walk, run and work without fatigue and had undergone within a few weeks a brusk body growth. However, there was no increase in body weight and the skin was still dry. Later reports by a qualified observer indicated progressive improvement along normal lines. The authors admit that thymectomy in a syndrome inexplicable on physical and endocrine grounds and presenting only slender clues to work on, in which other therapeutic measures have failed, must be regarded as a decision of desperation.

## Semana Médica, Buenos Aires

**47**:961-1028 (Oct. 31) 1940. **Partial Index**

*Treatment of Cervicitis by Mendez's Treatment of "Closed Cavity" for Immunity. R. Pastorini.—p. 994.
Vitamin C in Treatment of Hemorrhages. A. Carelli.—p. 1016.

**Mendez's Treatment of Cervicitis.**—Pastorini reports results obtained with vaccines prepared from bacterial haptenes and administered according to the "closed cavity" method of Mendez. References to this method of producing immunity were made in the Semana médica May 14, 1936 and Jan. 28, 1937 and abstracted in THE JOURNAL July 18, 1936 page 245 and March 27, 1937 page 1144, respectively. The merit of the treatment consists in maintaining the exudate of a given cavity in direct contact with local tissues. Organic exudates contain antibodies which, in association with the injected haptenes, stimulate a local reaction through which the exudates are rendered sterile. Haptenes of either gonococcic or pyogenic bacteria of the same type identified in the vaginal secretion are used in the treatment of cervicitis. The vaccine is injected into the wall of the neck of the uterus, one hour after intramuscular injection of 1 cc. of milk. Immediately after the injection of the vaccine, a suppository containing vaccine of the same type is left in the vagina and the latter is packed with sterile gauze, thus forming a local "closed cavity." The treatment is repeated at intervals of two or three days in cases of acute cervicitis and of four days in chronic cervicitis. Clinical and bacteriologic cure takes place after three or four injections in the majority of cases and after six or seven injections in the exceptional case. Follow-up of the late results of the treatment of 133 patients revealed that in a group of 121 who had had a complete treatment 115 obtained a permanent result. The treatment is harmless, economical, produces rapid satisfactory results and can be administered to pregnant and nonpregnant women.

## Münchener medizinische Wochenschrift, Munich

**87**:741-768 (July 12) 1940. **Partial Index**

Attitude Toward Treatment of Gas Edema. W. Wachsmuth.—p. 741.
Problem of Interruption of Pregnancy During Herpes Gestationis. J. Mayr.—p. 742.
*Causes of General Decalcification of Skeleton. H. Hellner.—p. 743.
Corpus Luteum Hemorrhage as Vital Indication for Operation. F. Pelmer.—p. 747.
Dosage of and Tolerance for Azosulfamide. E.-H. Garkisch.—p. 748.
Knee Phenomena and New Maneuver for Their Elicitation in Multiple Neuritis (Pseudotabes Polyneuritica). A. Knapp.—p. 749.

**General Decalcification of Skeleton.**—Hellner maintains that every generalized decalcification of the skeleton is due to a disturbance in the calcium-phosphorus metabolism. Osteogenesis imperfecta is a hereditary defect. The entire skeleton is deficient in calcium and is abnormally fragile. Since osteogenesis imperfecta develops in spite of an adequate calcium content of the food, a defective utilization of the calcium is assumed. It has been found that the calcium and phosphorus values of the serum are increased in osteogenesis imperfecta, but the activity of the osteoblasts is apparently defective. The fragility of the bones is accompanied by blue scleras, otosclerosis and occasionally disturbances in the development of the hair, the teeth and the nails, which indicates a hereditary impairment of the entire mesoblast. The hereditary defect may be apparent immediately after birth or it may become apparent later. Osteitis fibrosa generalisata is a form of skeletal decalcification which is due to endocrine disturbances, that is, to abnormal function of the parathyroids. However, the hypertrophy of the parathyroids is a secondary disturbance in skeletal decalcification, representing an effort at regulation of a disordered calcium content. Every disturbance in the calcium-phosphorus metabolism which is followed by decalcification of the skeleton influences the activity of the parathyroids and becomes manifest in their hyperplasia. This can be observed in osteomalacia, in rickets, in osteoporosis that develops in the presence of biliary fistulas, in Cushing's disease or renal and intestinal acidoses, in skeletal carcinoma, in multiple myelomas and in osteitis deformans. That hereditary constitutional factors play a part is proved by the occurrence of unilateral cases of osteitis fibrosa generalisata, for unilaterality can be only of genetic origin. Vitamin deficiencies may cause skeletal decalcifications, and the production of hormones is also largely dependent on adequate supplies of vitamins. Deficiency in vitamin D leads to skeletal decalcifications; rickets and osteomalacia are clinical manifestations of this. Decalcification of the skeleton in vitamin C deficiency is due to deficient osteoblastic activity. In the general skeletal decalcifications resulting from metabolic disturbances, acidosis plays an important part because the removal of excessive acids requires free calcium ions which are withdrawn from the skeleton. Disturbances in the intestinal absorption of calcium may likewise be a cause in general skeletal decalcification. Deficient absorption of calcium has been observed in pyloric stenosis and after total gastric resection. Osteoporosis, particularly of the spinal column, has been observed after prolonged use of laxatives. The etiology of skeletal decalcification varies widely. It is possible to differentiate between a hereditary disturbance in the skeletal utilization of calcium, a pathologic elimination of calcium from the skeleton, a deficient oral intake, a pathologic withdrawal from the skeleton as the result of metabolic disturbances or of an insufficient absorption in the intestine. Several of these disturbances may be combined. The treatment must consider the different etiologic factors.

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## CORRECTION

**"Pervitin."**—In the abstract of an article on Prophylaxis of Prolonged Coma in Insulin Shock by Accornero and Giordani in THE JOURNAL, Nov. 23, 1940, page 1835, reference was made to "1-phenol-2-methylaminopropanol." The correct name should have been "1-phenyl-methyl-aminopropane"—a drug apparently marketed in Germany under the name "Pervitin," manufactured by the Temmler-Werke, Vereinigte Chem. Fabriken, Berlin-Johannisthal, Germany. The Council on Pharmacy and Chemistry has found no evidence to show that the drug is available on the American market. Furthermore, under the new Food and Drug Act it would be necessary for the drug to be licensed for sale and interstate commerce. The preparation is related chemically to ephedrine, benzedrine and propadrine.

# THE STUDENT SECTION

of the

## Journal of the American Medical Association

*Devoted to the Educational Interests and Welfare of Medical Students, Interns and Residents in Hospitals*

SATURDAY, JANUARY 25, 1941


## A Study of the Medical Education of Women


KATE CAMPBELL HURD-MEAD, M.D.

HADDAM, CONN.


From century to century medical women as well as men have had interesting and important careers. There has been no age in which the two sexes have not worked side by side in order to improve the health and the happiness of the people around them as well as to augment their own fortunes.

### FROM THE FIRST TO THE FIFTEENTH CENTURY, A. D.

In the first century A. D., while Greek manuscripts were being translated into Latin, Soranus and Celsus and other learned men of Rome were making the hippocratic teachings in gynecology and pediatrics their own. A hundred or more years later Galen also copied and vastly increased what Soranus and Celsus had copied, but he used the medical material not only of other men but also of women doctors, among whom were an Aspasia, a Metrodora, a young Cleopatra and a little woman from Africa who was a classmate of Galen's in Alexandria.

In the eleventh and twelfth centuries came the heyday of the great coeducational medical school in Salerno, where men and women taught students from all over the known world and again interpreted old texts for them. Among the most popular teachers was a famous woman named Trotula, the mother of two brilliant sons and wife of Platearius, with whom she collaborated in several important volumes, compiled, doubtless, from extant remnants of Hippocrates and Galen and others to which, from their own experience, they added explanations and certain case records.

### THE TWELFTH AND THIRTEENTH CENTURIES

In the twelfth and thirteenth centuries at least two noted women wrote medical texts; one was a German abbess named Hildegard (1098-1179), of the Rhine region, the other a Greek princess in Constantinople named Anna Comnena (1083-1148). Hildegard had been well educated in medicine by her aunt and others in a famous German abbey. She became the friend and adviser of Saint Bernard and of three popes and two kings and was for many years the head of an abbey of her own on the Rhine. Hildegard wrote in poor Latin mixed with colloquial German. She not only treated patients so skilfully that they came to her from miles in every direction but her several medical books have been considered the best textbooks of the Middle Ages. Her botanic knowledge was phenomenal and her experimental methods of testing the value of her remedies were most advanced for the time.

Hildegard's contemporary Anna Comnena was a famous medical woman in far off Constantinople; she managed a great general hospital of a thousand beds as one of her duties during the early crusades. She was the daughter of the emperor, an expert physician, well trained by tutors. She wrote a great medical book containing many case histories, including a report of her father's last illness. She presided over the conferences of the physicians who were in the city in those years but whose names and deeds are now forgotten. Since she wrote in Greek and there was little call for translations from that language during the following centuries, her writings were forgotten but they are important medical texts, written by a medical woman.

A little later the skilled Abelard in Paris taught medicine to his beloved pupil and wife, Héloise. He even praised her as the most intelligent woman physician and surgeon in the country. She taught many pupils and gave her life for her humble patients.

### THE FIFTEENTH CENTURY

In the fifteenth century there were many educated women on the continent and in England studying medicine, collecting books and helping the poor and the sick. Among them was an Italian named Christine, from Pisa (1363-1431). Her mother was the daughter of the famous anatomist of the fourteenth century, Mondino, whose assistant was a young woman named

Alessandra Giliani, one of the first anatomists to inject the veins before dissections. As Mondino lectured she demonstrated the organs and tissues before his class. She died in 1326.

Christine's father was a physician and astrologer who was invited to the court of the French king as special consultant. He moved his family to Paris, where they were lodged in the royal palace, and there Christine, only a child, sat before the great library fire, curled up in a big chair browsing among the books and studying with the royal tutors. The "seven liberal arts" were the foundation of all education in those days, and medicine was included in the list.

She began writing poetry when very young, was a lover of Plato and Ovid, and became a strong feminist so soon as she read the tales in the Romance of the Rose and realized the inferior position given in them to women. She married the king's secretary, who appreciated her literary talents, and he urged her to write not only poems but essays on feminism, chivalry and pacifism. He and her father and the king all died as she was establishing her career and left Christine to support her two children and her mother and sisters by writing. This was a new role for women, and Christine's writings were very popular. She dreamed of a Utopia in which women were able to show their superiority and she produced a great work entitled The City of Women, in which she extolled all the great women of antiquity and then showed the glory of a city built entirely by women surrounded by a wall as high as that of Carcassonne, in which were schools and hospitals and churches, women physicians, surgeons, teachers, lawyers and preachers. She also wrote of military tactics, medicine and charity. Her admiration for Joan of Arc knew no bounds, but her own spirit failed when Joan was imprisoned and killed. She retired to a convent to practice the seven works of mercy for the sick and infirm, and showed mothers how to care for their children and how to feed their families in a wholesome way. Her only poem in those days was a eulogy on Joan of Arc in which are the well known lines

> God knew well how to create great women
> Since He created thee.

Christine da Pisa was an outstanding example of the educated medical student of the fifteenth century.

### THE SIXTEENTH CENTURY

In the sixteenth century, as has been already hinted, the famous Italian physician and Greek scholar Linacre, from the medical school of Padua, was invited to London to become one of the royal physicians and tutors at the court of Henry VIII, among whose friends were Erasmus, Sir Thomas More and Cardinal Wolsey.

When the College of Physicians was founded, Linacre opened his house as a coeducational medical school, near St. Paul's Cathedral. We may suppose that the two daughters of Sir Thomas More were among the first pupils. Margaret More married her private medical tutor, Dr. Roper, and Margaret Giggs, her foster sister, married her tutor, Dr. Clements. Both men were physicians to King Henry and Queen Catherine. Troublesome times, nevertheless, were ahead for Sir Thomas More and his friends over the question of Henry's first divorce, and one after another of the royal advisers was imprisoned and killed. The More women soon had to use all their medical skill in treating the sick, and the two Margarets cared for Sir Thomas in prison before the headsman's ax fell. The prisons were filthy, the homes of the poor were like sties, and when the plague raged misery reigned everywhere.

Many women of the nobility, the mother of Sir Francis Bacon, for example, studied and practiced medicine. Linacre lectured at the great universities and he upheld medical women, but gradually he gave his time to the Greek language rather than to medicine. Henry kept on with his marital program but provided his daughters Mary and Elizabeth as well as his only son with medical tutors so that they might advise even the bishops as to things medical.

### THE SEVENTEENTH CENTURY

Louyse Bourgeois le Boursier was the wife of a barber surgeon in Paris whom she had learned to assist in his operations and even to take his place in emergencies. He died young, leaving her with two children. She applied to her friend Paré for more teaching but he advised her to specialize in midwifery. He lent her his newest books and gave her many ideas as to technic. She was so apt a student that he recommended her to the queen, Marie de Medici, and she was immediately engaged as royal accoucheuse.

Louyse Bourgeois not only cared for the queen in all her seven confinements but was midwife in chief to the ladies of the court, refusing to do abortions for any woman at any price, and producing living babies where sterility or dead infants had previously been the rule. She practiced in Paris for many years and wrote the best book on obstetrics ever printed—a work which she dedicated to her daughter.[1] The Rose Gar-

1. Louyse Bourgeois's writings have a very modern ring although here and there she lapses into contemporary pseudoscience. One of her books begins "As it is not the duty of women to write books I never would have undertaken it but for the urge of the administrators of the Hôtel Dieu. . . . I have had a repugnance to the publication of my methods and observations for fear that they will be used as a short-cut to becoming a sage femme without sufficient training." Louyse also hopes no one will think her egoistic for writing her experiences and putting her advice on paper.

den of Roeslin was thus superseded and Louyse's volume went through many editions. She died in 1638, and historians call her the first really modern obstetrician. She showed great skill in manipulating versions in difficult birth, and because of her special cleanliness she lost very few patients from puerperal fever.

Louyse Bourgeois was followed by Marguerite Leboursier du Coudray, her grand-daughter, who, together with another of Louyse's pupils, Marguerite du Tertre de la Marche, became famous teachers and supervisors of obstetrics at the Hôtel Dieu in Paris for many years. Mme. Boivin, one of their pupils, carried their traditions into the eighteenth century. Mme. Dugés and her daughter Marie Louise Dugés-Lachapelle carried the teaching still further into the early nineteenth century, when many men physicians from Europe and America studied in Paris with these famous women. They all wrote excellent textbooks which went through many editions up to 1824, quite eclipsing the works of Mauriceau and Baudelocque. To those women the Chamberlen forceps was both unnecessary and dangerous. They knew not why the use of these instruments should be followed by puerperal fever, but they discarded them. The University of Marburg bestowed an honorary M.D. on Mme. Boivin for her excellent work.

Surgery, despite the teachings of Ambroise Paré, was in the main relegated to women and quacks in Europe during the seventeenth century. They couched for cataract under any tree; they operated for stone and removed tumors wherever they found a patient. Hernias and compound fractures were everyday surgery, and it was cheaper to pay a fine than to get a license. Not until A. D. 1800 was the College of Surgeons founded in England, and surgery then began to emerge from under the authority of the physicians.

One example of an English woman of noble birth who became a capable physician and surgeon in the seventeenth century through her mother's teachings and the oversight of medical tutors was Anne Murray. About 1649 she was "wounded in love and hoped to die." She said that she "laid some hours speechlesse," then she "began to gape and bethought her of her own cordialls," and "her speritts revived." She soon married Sir James Halkett, despite her badly pock-marked face. She had four children, three of whom died in infancy. With her husband, an army officer, Lady Halkett went to the battle of Dunbar in 1650 so as to care for the wounded soldiers. She "saved sixty badly mangled men," for which the king gave her "fifty pieces of money." Her later medical career was extraordinarily successful, and patients flocked to her from all over the country. Lady Halkett was not only a very successful surgeon and writer of medical books but a preacher and writer of religious tracts and books, twenty-one volumes in all. She died in 1699, full of honors, at a ripe old age.

Two more English women surgeons should be cited because of their excellent work. One was Elizabeth, countess of Kent, who published a popular work on physic and surgery from her own experiences in 1670. This was republished in England and translated into German and published in Germany. The other was Catherine Bowles, famous for her comparatively painless operations for hernia and stone in the bladder. There was no really painless surgery in those days, although opium and whisky were freely used. The nauseating "solvent" for stone, a remedy invented and widely advertised by a clever woman impostor, Jane Stevens, was bought by trusting sufferers at great price, and the prescription for its preparation of soap and lime and what-not was bought by parliament for an enormous sum, ostensibly for the use of the poor, but most of the patients found the treatment worse than surgery and of no actual benefit.

### THE EIGHTEENTH CENTURY

The eighteenth century has given us the biographies of many clever medical women in every country.[2] Of them all, however, only one woman was mentioned in Mrs. Sarah Josepha Hale's[3] great encyclopedic Woman's Record published in America in 1853. She was Maria Delle Donne of Italy, born in 1776, a woman admired and honored by Napoleon for her remarkable obstetric work in Bologna, where she was a professor in the university. She died in 1842 and her death was recorded throughout Europe and America.

### THE NINETEENTH CENTURY: MEDICAL EDUCATION OF WOMEN

I have shown that even before the nineteenth century many women practiced medicine in every generation with as much success as though they had had a university education, but it would have been good for both men and women to have wider training.

In 1847 Elizabeth Blackwell, who had been studying medicine privately with medical teachers, as most men studied in those years, applied for admission to nearly a dozen American medical schools, but only one, in Geneva, N. Y., was opened to her, as more or less of an experiment. This was a "regular" medical school, nonsectarian, but through no fault of hers it was promptly closed to women after Elizabeth's graduation, when various regular and irregular schools admitted women.

2. Mead, Kate C. Hurd-: A History of Women in Medicine, Haddam, Conn., Haddam Press, 1938.
3. Hale, Sarah Josepha: Sketches of All Distinguished Women from the Beginning till A. D. 1850. In Four Eras, with Portraits, 1853.

In other countries medical education was opened to women as follows: Switzerland 1864, Paris 1867, Sweden 1870, the Netherlands 1873, Denmark 1875, Russia (temporarily) 1876, Italy (as a demonstration) 1877, London 1877, Spain 1881, Scotland 1886, Belgium 1890, Portugal 1897, Austria 1897, Germany 1900.

Although women were never actually excluded from the Italian universities if they were prepared for their courses, few did apply, and it is said that women might have been admitted to all Scandinavian medical schools after 1870 had they applied there. In Russia the government of the nineteenth century played fast and loose with women students not because they feared for the health of girls but because of the changeable political conditions in the country. Men and women nihilists were routed out of their classes at the university on slight pretext. Many of them, therefore, went to Switzerland in the sixties to study medicine, for doctors were sadly needed. In several Swiss cantons the universities were opened to women as soon as there were fitting applicants, but many of the pioneer Russian women students were among those called home by the czar in 1874 and sent to Siberia as traitors.

Even in the free land of America, however, it had been difficult for either men or women to get an adequate premedical education in the first half of the nineteenth century. In 1846 a midwifery school was opened in Boston to prepare women for obstetric work because of the "indelicacy" of having to employ men midwives in labor cases. Before 1830, on the other hand, when most of the medical schols were privately owned, one or two men gave all the courses to unprepared students (men), but as early as 1760 a New York law had been passed regulating the practice of medicine and making it imperative that a physician should be examined for a license to practice by "His Majesty's Counsel or a Judge of the Supreme Court and the King's Attorney General and the Mayor of the City or any three of them." This was only locally obeyed. Benjamin Franklin advised men to go to Edinburgh for a degree, and many rich men took his advice.

Medical education was still in confusion when Elizabeth Blackwell was admitted to the medical school in Geneva, N. Y., and it has been difficult for biographers to evaluate the lives of the then practicing American doctors according to estimates by their colleagues rather than by those of admiring patients or obituary records in newspapers. Nevertheless, the remarkable work of Kelly and Burrage [4] is a mine for biography hunters and saves many a long and tiresome research. Judged by the standards of this great work a man or a woman included in the text must have been not only an outstanding doctor or credited with considerable public work or a discoverer of some new method of treatment, a sanitarian, a teacher, a remarkable surgeon or a good writer or lecturer and prominent in scientific or medical circles. Fortunately there are many medical women included in these biographies and in encyclopedias of various kinds. From such sources as well as in certain popular local histories and libraries we find the biographies of important medical women. Fortunately, academies and seminaries had already been opened to young women of eastern America by scholarly women even before the eighteen thirties, when Oberlin and Antioch colleges became coeducational. Mary Lyon founded a seminary in South Hadley, Mass., for women who wished to become teachers or missionaries, and Miss Willard's school in Troy, N. Y., and Dummer and Ipswich academies in Massachusetts and several Moravian schools had been opened for "healthy and happy Christian young women."

Railroad travel was very limited before 1850 and considered an adventurous undertaking. Ordinary journeys were made by carriage over bad roads or on horseback through long stretches of lonely country in the "far west," even to Pittsburgh; mountains were fearsome, and swollen river fords dangerous. In 1825 the first railway train was driven over a small stretch of country in England, and the train from Albany to Schenectady was an experiment in 1830. Quarantine for contagious diseases was lax before 1840, and the general mortality of all classes and all ages was high until there was effective cooperation between state boards of health and the public health service at that time.

Judged by the standards of the American Medical Association, when taken in connection with the general advance in preparatory education of women, one finds them after the eighteen fifties ready to undertake the study and practice not only of general medicine but of every special branch of medical science, so that fifty years later, when many new departments had come to be included in a medical curriculum, there was as diversified scope for women's talents as for those of men, and one notes the names of such specialists as Alice Hamilton in industrial diseases, Carroll Birch in blood dyscrasias, Florence Rena-Sabin in anatomy and histology, Ellen Potter in public health, Josephine Baker in sanitary work to decrease infant mortality, Gladys Dick in the diagnosis of contagious diseases, Catharine Macfarlane, Bertha Van Hoosen and Lilian K. P. Farrar in surgery, Anna Broomall and Rachel Yarros in obstetrics, and Priscilla White in diabetes.

4. Kelly, H. A., and Burrage, W. L.: American Medical Biographies, Baltimore, Norman, Remington Company, 1920.

MEDICAL SCHOOLS ADMITTING WOMEN

In 1900 there were 162 medical schools of all grades in the United States, but by 1935 there were only seventy-seven class A schools still in existence, so sweeping had been the work of the American Medical Association in eliminating inferior and proprietary schools while elevating the general level of medical education. Fortunately, the Women's Medical College of Pennsylvania was among the number still in existence, and most of the state universities were coeducational.

In the earlier days, when the American Medical Association was revivified (in 1847), many innovations were occurring among women's organizations. The first woman's suffrage convention was held at Seneca Falls, N. Y., in 1848. Elizabeth Blackwell was then a senior at the Geneva, N. Y., Medical School, antislavery and temperance and missionary societies were swinging into line, and women were beginning to preach and to study law as well as medicine.

Elizabeth Blackwell, as has been said, was graduated in 1849 and her sister Emily in 1854, and the Woman's Medical College of Philadelphia was founded in 1850. Both of the Blackwells and many graduates of the Philadelphia and Boston schools went to Europe to study after receiving diplomas in the United States. But aids in diagnosis were rare.

Students had no microscopes, no stethoscopes, no clinical thermometers, no ideas of antisepsis or of the role of bacteria, and no personal knowledge of anesthetics for the elimination of pain during surgical operations or during labor, but the numbers of medical women increased rapidly.

In 1940 we find the following astonishing statistics taken from the United States Census by Dr. Louise Tayler-Jones [5] of Washington, D. C.: In 1870 the number of registered medical women was 527, in 1880 2,432, in 1890 4,557 and in 1900 7,387. Since then women have been graduated from medical schools as, roughly, 4 to 5 per cent of the men graduates; i. e., in 1905 there were 1,073 women in medical schools, or 4.1 per cent of the number of men; in 1915 there were only 592, or 4 per cent, in 1925 910, or 5 per cent and in 1935 1,077, or 4.7 per cent. Various reasons were given for these data, such as the house cleaning of medical schools by the American Medical Association—diploma mills being excluded—which reduced the number of schools from two hundred to one hundred, after the admirable survey by Abraham Flexner.

In 1937 there were only seven medical schools in the United States which did not admit women, and only one which did not admit men except to its staff of professors.

Most colleges now require at least three years' premedical course, and more than half of the women students are college graduates—all require one year's internship before registration for practice and before taking the state or National Board examinations.

Another fact, however, is significant: Among 712 hospitals approved by the American Medical Association only 105 have internships open to women, but even there it is not always easy for a woman to secure a good rotating service, especially in surgery.

The old and worn out statement that diploma'd medical women marry and do not practice has been proved quite incorrect and may be a wishful thought of the anti-woman intern medical man; but statistics show that, although one third of the women do marry and have families, very few fail to practice.

Among the early pioneer medical men and women were many "irregulars," if judged by university standards. Undoubtedly certain "pathies" seemed reasonable to certain people. There were water cure institutions which graduated both men and women, and eclectic schools, and hydro-electro concerns, and vegetarian and Thomsonian schools, as well as popular Homeopathic colleges like that of Dr. Clemence Sophia Lozier in New York City, which was of high grade in its own pathy and which flourished in reaction against the enormous and poisonous dosage of some of the "regular" schools. In the middle of the nineteenth century, surgery was a matter of speed and luck, since "laudable pus" was expected to follow any wound, and anesthetics were still experimental; but many women soon became excellent surgeons.

Such conditions still prevailed up to the eighties, while medical women grew mentally and scientifically as rapidly as men and kept shoulder to shoulder with them in education and practice. Nor did their health suffer from their heavy work but quite the contrary happened, as Dr. Elizabeth Bass of Tulane University has recently shown, and many of the most prominent women in medical circles died of old age: Elizabeth Blackwell at 89, Emily Blackwell at 84, Elizabeth Cushier, teacher, surgeon, obstetrician, at 94, Marie Zakrzewska at 73. The British medical women were as long lived. But few medical women in any country failed to earn a good living, and many of them brought up large families, among whom might be mentioned Hannah Longshore, Mary Frame Thomas, Mrs. Dolley, Mrs. De Hart and Madame Lozier in America as well as Elizabeth Garrett Anderson in England. They raised their families, practiced medicine most successfully, did magnificent public service, and died at as ripe an old age as the unmarried women doctors.

5. Jones, Louise Tayler-: Medicine as a Field for Women, J. Assn. of University Women, 1938.

### BIOGRAPHIC NOTES

Fortunately it is becoming somewhat easier, as the years roll on, to collect the biographic histories of medical women in various countries. Beginning with Glances and Glimpses, or the autobiography of Harriot K. Hunt of Boston, early in the nineteenth century, one turns to Elizabeth Blackwell's autobiography and to that of Marie Zakrzewska, compiled from her own diaries by Dr. Agnes Vietor, and to Mary Putnam-Jacobi's life and works prepared by her niece, and to Emily Blackwell's career by Dr. Annie Daniel, and Ann Preston's life and that of other early teachers in Philadelphia as written by the successive deans of the Women's Medical College of Pennsylvania, and many others in every country, biographies which add immeasurably to the historical value of medical history though they have been overlooked by men historians. Naturally there are still many lacunae in every state and country which must be filled by willing workers.

We are indebted to Dr. Victor Robinson for publishing biographies and a general history of medical women, in the *Medical Review of Reviews* and to Dr. F. C. Waite of Western Reserve University for his articles on the early medical schools of the United States, including the biographies of the earliest women members of the early coeducational schools, and to the *Medical Woman's Journal* and the publications of the medical women's associations in America and Europe which have appeared since the founding of national associations of medical women during the war of 1914-1918 and subsequently.

It is fortunate that men and women differ in their outlook on life but unfortunate that women should still find it difficult to win adequate recognition for their talents and to obtain adequate internships. Opportunely Bellevue Hospital in New York now has thirty-two women interns on its staff and the Philadelphia General Hospital has nearly as many more, while the hospitals for women in several of our large cities also take many women interns; but there is in fact a serious shortage of adequate positions for women interns, since they as well as men must have rotating hospital service in class A hospitals before obtaining license to practice, but, as hospitals are supported by the public, women should be appointed to hospital posts on the same terms as are men, entirely without regard to sex, especially in states which demand internships before taking state examinations. Lately, however, has come an appeal from one Louisiana maternity hospital for women applicants who wish to specialize in obstetrics. Many small hospitals approved by the American Medical Association are said not to have had women applicants although offering internships to them.

During the existence of the New York Infirmary Medical School for Women and its thirty years of teaching it sent forth hundreds of able women as well trained as any men or women in the world.[6] Its graduates have been successful in practice in foreign fields as well as at home, many have become famous surgeons and x-ray specialists, and others have made important laboratory investigations in cancer, bacteriology and public health work. Its first class was graduated in 1870 by the Blackwells, and a class went out each year until 1899, when it united with the Cornell University Medical College.

It is evident, therefore, that there can be no differentiation between the sexes in medical study or practice and that neither in the United States nor in England was any distinction thought necessary by the founders of the medical schools for women. The old Boston (Gregory) medical school for women was united with Boston University after about thirty years of teaching, and the Chicago school was united with the Northwestern University eventually, not because of failures in their students or inability to balance their budgets but because it is economically beneficial to combine the expensive paraphernalia of buildings, equipment and staff in one or more large institutions.

The Woman's Medical College of Philadelphia and the London, Royal Free Hospital School of Medicine for Women, however, have continued with their original purpose in order to give opportunity for women as professors and more intensive education for women in gynecology, obstetrics and surgery than they could obtain in a man's college; they should also insure a solidarity among medical women like that which has been held by men since the earliest times. In every case, however, medical women have been assisted by the noblest of medical men in attaining their aims and in founding medical schools and hospitals for their needs as well as in the practice of medicine.

Among the first coeducational medical schools was the University of Michigan Medical School, which graduated its first medical woman, Dr. Amanda Sanford, in 1869. Since then it has graduated hundreds of women of whom the university has been proud.[7]

### WOMAN FOUNDERS OF HOSPITALS AND TEACHERS

Many of the early woman graduates of the medical schools in the United States founded hospitals or dispensaries for women and children soon after their own graduation. The New England Hospital for Women and Children in Boston was founded by Marie Zakrzewska,

6. Daniel, Annie S.: A Cautious Experiment, M. Woman's J. **46**: 125 (May) 1939 and subsequent issues.

7. Selman, Bertha: Medical Women in Michigan, M. Woman's Quart., 1940.

M.D., Cleveland, 1856; the New York Infirmary by Elizabeth Blackwell, M.D., Geneva, 1849, and her sister Emily, M.D., Cleveland, 1854; the Detroit Woman's Hospital and Foundling Institute by Sarah A. Gertrude Banks, M.D., University of Michigan Medical School, 1873; the Woman's Hospital in Philadelphia by Ann Preston, M.D., Woman's Medical College of Pennsylvania, 1852; the San Francisco Hospital for Women and Children by Dr. Charlotte Blake Brown, who had been an intern at the New England Hospital in the early seventies.

Such a list could be shown in England and Scotland, where Elizabeth Garrett-Anderson's large hospital in London grew out of her dispensary opened in 1864. Sophia Jex Blake's hospital and medical school was founded in the early eighties in Edinburgh because of the demands for the medical education of women in Scotland. The Royal Free Hospital in London, connected with the medical school for women, became a teaching hospital in 1877 as the result of the energetic work of the women pioneers and their friends, and it still grows.

In the nineteen thirties one finds here and there successful women doctors teaching in coeducational medical schools, few, however, having "full chairs." At the same time there were sixty-eight women on the staff of the Woman's Medical College of Pennsylvania, twelve being full professors in surgery, obstetrics, gynecology or pediatrics. The graduates of this college have seldom failed to fill hospital as well as teaching positions with honor, and they have had but few failures in examinations for state licenses or internships.

The governors of Old Blockley Hospital in Philadelphia have always been fair to women candidates. In 1883 Dr. Pauline Root was the first woman to win an internship there, and she had a most valuable training preparatory to entering missionary work in the south of India. Even in the forties and early fifties Elizabeth Blackwell and Sarah Adamson (Dolley) were given the privileges of the obstetric wards at Blockley.

In New York City in the late sixties Dr. Emily Blackwell and Dr. Sophia Lozier led their students to the wards and lectures at Bellevue Hospital, where, many years later, Dr. Emily Dunning (Barringer) of the Infirmary School was the first woman intern and ambulance surgeon.

When Mary Putnam (Jacobi) returned from Paris in 1871 with her French diploma she was at once accepted as visiting physician at Mount Sinai Hospital, which has never closed its doors to women.[8]

8. Unfortunately, no woman was appointed to the early staff of the Woman's Hospital in New York City, although women had been instrumental in founding it and had been given a promise from Dr. Marion Sims, its surgeon, that a medical woman would be resident physician there. Various excuses failed to soften the blow to women doctors or their cause because of his failure to keep his promise.

Beginning with the founding of women's hospitals by woman doctors the training of nurses has been continuous and valuable. In the Philadelphia Woman's Hospital, connected with the medical school, Dr. Ann Preston and Dr. Emmeline Cleveland in 1863 organized a regular course of lectures and practice for woman nurses. This was continued by Dr. Edwin B. Fussell and Dr. Mary Scarlett-Dixon, and student nurses received certificates after severe examinations. It has had a steady growth.

The nursing school in the New England Hospital, Boston, under Dr. Susan Dimock, Marie Zakrzewska and others was the first to be chartered. From this school Linda Richards in 1872 received the first diploma ever granted a nurse in this country. She eventually organized several other schools, and Yale and Bellevue soon followed, bringing in their train those of Dr. Gertrude Banks in Detroit and Dr. Charlotte Brown in San Francisco.

Woman student pioneers in coeducational medical schools have generally won prizes or prize positions for interns by competitive examinations. Mary Elizabeth Bates of Colorado won the first position as intern at the Cook County Hospital in Chicago, but she was subjected to many annoyances on that account. Edith Pechey Phipson, an extramural student at Edinburgh University, 1869-1872, won a coveted chemistry prize but it was not awarded to her. Woman doctors in those days were often subjected to impolite attentions by the public in general but gradually they were accepted simply as "queer." This attitude has been followed by one of indifference, which has perhaps been harder to overcome and is also vanishing.

Woman surgeons have perhaps had the hardest struggle for recognition. Among the pioneer woman surgeons in America was Elizabeth Cushier, who performed major operations at the New York Infirmary for twenty-five years with as great success as was achieved by Marion Sims and Emmett and other noted men. Elizabeth Keller and Fanny Berlin operated at the New England Hospital in the eighties, and their laparotomies gave them great credit. Charlotte Blake-Brown in San Francisco performed the first successful ovariotomy on the Pacific Coast. Hannah Thompson in Chicago operated for many years as cleverly as did the men of the largest hospitals. Anna Broomwall and Hannah Croasdale followed Emmeline Cleveland as surgeons at the Woman's Hospital in Philadelphia without the least adverse criticism.

Women as medical lecturers on physiology and hygiene have been generally accepted by the public from their earliest years without opposition until, following Dr. Hannah Stone and Dr. Valeria Parker, they began to teach sex hygiene and to point out the possibilities

and advantages of conception control and the prevention of venereal diseases. This has brought them many stanch defenders as well as opponents among the medical men. Fortunately the subject is now bravely furthered in *Hygeia* by the American Medical Association's editorial staff and by noted men such as Drs. Parran, Flexner, Fishbein, Robert Latou Dickinson and C.-E. A. Winslow.

### WOMAN AUTHORS AND WOMEN IN IMPORTANT POSITIONS

Many medical women have written successful books on hygiene and public health, beginning with those by Dr. Harriot K. Hunt of Boston, Elizabeth Blackwell of New York, Elizabeth Garrett and Sophia Jex Blake of London and others leading up to those of Dr. Belle Wood-Comstock of California, Dr. Lena Sadler of Chicago, Dr. Josephine Baker of New York, Dr. Lulu Hunt Peters, Dr. Josephine Jackson and others.

Several women have had important positions as heads of city, county or state departments of health, among whom the earliest was Dr. Mary Frame Thomas, city physician in an Indiana town in the sixties, Dr. Mary R. Butin of Madera County, Calif., head of the county department of health in 1902-1913, and Dr. Esther Pohl Lovejoy, chief of the State Board of Health of Oregon, 1907-1909. Many other medical women have filled similar important position, among whom may be mentioned Dr. Ellen Potter in New Jersey and Dr. Martha Tracy and Dr. Mary Riggs Noble in Pennsylvania.

Unfortunately, few medical women have had the honor of membership in the House of Delegates of the American Medical Association, although many have been officers of their state and county associations. This is regrettable since the double point of view of males and females provides for the elimination of many errors in judgment. Dr. Sarah Hackett Stevenson caused no little consternation when the Illinois State Medical Society sent her as a delegate to the annual session of the Association in Philadelphia in 1876, but she was accepted politely and apparently did no harm! Since then, however, she has had few followers. Among the fortunate few are Drs. Frances Rutherford and Marie E. Greene of Michigan, Dr. Martha Welpton and Dr. Mary R. Butin of California and Dr. Emily Dunning Barringer of New York, but woman members of the Association feel that they should be continuously represented among the delegates, since there is no longer a question of sex in medicine and minorities should always be able to express their views in any association doing business of any kind. This was the theme of an address given by the President of the Association, Dr. Ray Lyman Wilbur, in 1923 at the San Francisco meeting of the Medical Women's National Association. Unfortunately, however, medical women are not as a whole politically minded or insistent on their privileges even in minorities.

Since the organization of the International Association of Medical Women in 1919 it has been found all over the world that woman doctors have the same high ideals, the same kind of mentality, the same general objectives, unselfishly working to reduce physical suffering and lessen morbidity and mortality and therefore to eliminate crime and misery. Better still, they are working in similar ways and with similar instruments. They understand one another no matter what language they talk, for the education of women, like that of medical men, is the same the world over.

There is no place on the globe so hot, so cold, so dreary, so miasmatic, where women doctors have not worked as hard and intelligently as men. Women doctors are found among the starving populations in China, the fanatical castes of India, the aborigines of Central Africa and the unlettered natives of South America as well as in the slums of the great cities of the world.

Through the American Women's Hospitals' Committee of the National Medical Women's Association, financial aid and medical personnel have been sent to all the warring countries during war and reconstruction. Woman doctors have traveled with ambulances and dispensaries and opened clinics or temporary hospitals wherever the ravages of war have made such help necessary. At the present time (midsummer of 1940) medical women are on the battlefields in the warring countries and are being materially aided by the medical women of the United States and Great Britain.

In several of the Southeastern states medical women and nurses are working under the American Women's Hospitals' Committee of the Association of American Medical Women to improve the health of the mountain whites. The personnel is maintained in conjunction with the boards of health of the contiguous counties to provide prematernity and child welfare care, as well as good obstetrics, in localities far from the city hospitals, and also to provide proper dietaries for tuberculous invalids and to aid in the elimination of hookworm and beriberi, carrying on the work by means of traveling dispensaries and clinics, teaching home nursing and first aid, and doing whatever is needed to improve the health and working efficiency of these neglected white people. Thus the field of service for medical women continually widens.

CONCLUSION

Finally, I must close this tightly compressed article hoping that the vision of some medical students has been sharpened to look still further into the detailed history of medical women and also to preserve the records of the quiet and self-effacing women in the profession who are content to do careful and scientific work for their patients without the blare of trumpets. Surgeons like Dr. Gertrude Herzfelt in Edinburgh and Louisa Martindale in London, obstetricians like Dr. Joan Rose in Scotland and Dame Louisa MacIlroy in England have their prototypes in the large cities of the United States. Women should be proud to belong to such a noble profession, and unite to uphold it with all their might, while realizing that in medicine as in music the pauses and silent spaces are as important for them as the trumpet notes, but insisting on the generosity of the majority to the minority of the medical practitioners, and by union of well trained women to prove that it is quality, not numbers, that counts.

# British Students Carry on After Bombing of St. Thomas's Medical School

St. Thomas's Hospital Medical School in London, one of the most famous medical schools in the world, has been evacuated following several attacks by German bombers. New arrangements were quickly made, however, for the students to carry on their studies elsewhere. The preclinical subjects and pathology are now being taught in Godalming, where the premises of a girls' school and other buildings have been taken over for teaching and billeting purposes. The senior students are centered at Guildford, while the other clinical courses are centered in several hospitals throughout the sector.

In the December *St. Thomas's Hospital Gazette,* students write of the experience. Several students who at first went to the roof of the hospital to watch some thirty German bombers, beat a hasty retreat when a large whistling bomb fell within a mile of the hospital. They slept in the basement that night and in the early hours of the morning were awakened by a terrific crash. Hurriedly they made their way to the corridor to be met by a wall of smoke, dust and fumes. A block of the hospital had been hit. They stood aghast at the damage for a second, then organized a searching party and went through the building to remove from the rubbish the sick and invalid. When daylight came it was revealed in the shambles that none of the patients had been hurt, although all in Adelaide had to be removed to the shelter of Edward. A nurse and a masseuse were still buried among the ruins and believed to be still alive. Rescue squads were trying to save them. The ward patients were carried downstairs in their beds to the basement for safety. Can anyone imagine, they ask, how much staying power it takes to carry a heavy man downstairs in his bed and insure that his suprapubic drainage is intact when he gets to the bottom? All other patients were evacuated the next day to their homes if well enough or to the sector. Although they were tired when this task was done, the cheerfulness of the sisters and nursing staff and their constant activity to help others were incredible.

The medical students had to find other quarters for the night and on the following day were assigned quarters in the roentgen ray department, where they carried their mattresses. A piano was put in the corridor at the entrance to the department, a sing-song was organized and an informal party enjoyed until 10:30, when all went to bed. In the early hours of the next morning another terrific crash occurred and débris came clear through the hospital to the basement, causing some casualties and necessitating many readjustments. The students believed that their "mattress barriers" on this occasion saved their lives. As the hospital accommodations were now much reduced, and it would be better, some of the students went home.

A few days later a large bomb hit College Hospital and went clear through to the basement before exploding, causing three deaths. Never before have medical students and physicians been able to see the real worth of the Nightingale training and the women from whom nurses are drawn. Bombed out, blasted from their quarters, and some losing all they had, the sisters and nurses kept on working to make others comfortable. The hospital was falling in parts about their eyes.

Accommodations for the first, second and third year students were now found at a new location in Surrey, where they were quickly able to settle down to work in dormitories (those of a former girls' school) and with reading and dining rooms and some of the atmosphere of a club. Some of the students lived in private billets. The various departments were housed here and there, the physiology and pathology sections in stables, which is not as bad as it sounds. The anatomy department acquired a squash court to be used for dissections. Here specimens for a time were at the mercy of the elements, but plans went forward quickly for the building of huts for this department. The

biology, physics and chemistry departments had part time use of the laboratories of a neighboring public school, and their clinical teachers come down to lecture and take the students for ward rounds twice a week elsewhere in the sector. They receive visits from Mr. Robb, who talks about surgery, Dr. Petch, who talks about medicine, Dr. Thomson, who takes them for ward rounds, and Dr. Bamforth, who comes frequently to talk about the blood.

The other student activities, they write, continue much as they did at St. Thomas's. There is a vigorous soccer team and a rugger team. On the whole, they are having a remarkably good time. Other students write of having arrived at St. Thomas's after a third bomb had registered, making it probably necessary that they should have to look to the sector until the war was over. Students who were fortunate enough to be doing gynecology came out to the country base in the sector, where they were welcomed as men rescued from the front line trenches, Mrs. Milligan refreshing them with sherry and tea and Mr. Wyatt having billets awaiting them so that their medical lectures and other classes began at once at the Warren Road hutments. The country club even admitted some of them as special members, and the golf club halved its fees. More students arrived from time to time until there were one hundred altogether. An empty shop was used as a lecture room, and the volunteers who ran it probably enjoyed the lectures, which they heard through the partition as they prepared lunch.

A Red Cross room in the county hospital was lent for classes in medicine and surgery, and the courses in the special departments and in gynecology were held at the county hospital and at Warren Road. A second vacant shop was acquired to serve as both library and lecture room. They were not prevented from having tea with the 4 o'clock classes, even though the teachers might occasionally be unable to reach the class. Thanks to the energy of all the neighbors, they had a fair chance of carrying on their work and of dealing with imminent examinations. The students feel that much praise is due those responsible for the hospital arrangement and the billeting scheme under these conditions. Their only criticism might be that perhaps a little more of their time should be allowed in the outpatient department.

Some members of the teaching staff—four surgeons and nine physicians—find that the new surroundings offer many of the advantages of London plus the benefits of living in the country. They share their courses, including ward rounds, lectures on therapeutics and a weekly pathology drive, while operations are performed every other day. Surgical cases are numerous, but a medical case is a rarity. They have partial freedom of the M. O.'s house, where they gather as they did at St. Thomas's House, and they are becoming most virile here where Hitler seems little more than a buzz in the sky.

The trauma unit has the largest clinic in the hospital. Instruction in traumatic surgery is given at all times of the day and night. Different members of the staff react to the presence of the students in different ways, most of them not unfavorably. The students find inevitably "in the excellent and enthusiastic teaching" similarity and contrasts with the former days at St. Thomas's.

Another student writes that six of them arrived at the hospital in the sector to act as paid members of a mobile ambulance unit for one month, consisting of a doctor, six nurses, two male attendants and two vans provided by the American Red Cross. They were on call to be immediately available in pairs for twenty-four hours at a time. Most of their days were given to normal hospital routine, attending clinics, operations and necropsies. Their only criticism was the exceeding thinness of the roofs above them and the want of a tin hat for each of them. The sleeping quarters for this group was a problem, as they did not fancy living on the first floor. One night their room was shared with a corpse, which they put up with; but, when more of them came, four of the students were crowded out and they returned to Surrey. The other two remained to deliver any available babies and to hope for signs of activity by their ambulance.

The *Gazette* adds that the whole school owes a tremendous debt to the school authorities for the speed and skill with which arrangements for carrying out instructions and medical care were completed, a process which has been greatly aided by the kindly cooperation of the medical officer of health for Surrey and his staff and the various medical superintendents.

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**Delicious Moment.**—One of the most exciting moments in the medical student's career is that in which, with the examinations in anatomy and physiology just behind him, he first enters the wards of a hospital. Now, after two or three years of apparently getting nowhere, he feels that he has at last got his foot upon the good hard road of medicine. He sallies forth into the town and buys a stethoscope—delicious moment! He hurries home and then, withdrawing to his room, tremulously applies the instrument to his chest. Cavernous, incomprehensible rumblings meet his ear. This—will one ever be able to make sense of this? Is this poor thing the long-awaited voice of professional destiny? The instant doubt is quick forgotten; the next adventure hurries on; in the morning, magnificently armed with the seal and emblem of his trade, he takes his place at the bedside—his first patient before him, his mentor gazing at him across the bed. . . . But, as the time goes by, the boundaries of medicine's cultivated lands force themselves upon the initiate's attention. Beyond them he sees the vast unbroken territories in which disease runs wild.—Bateman, Donald: Berkeley Moynihan—Surgeon, New York, Macmillan Company, 1940.

# Digest and Reviews

## THE SELECTION OF MEDICAL STUDENTS AT MINNESOTA

*Abridgment of an article by Dr. C. D. Creevy, assistant dean, University of Minnesota Medical School, published in the Bulletin of the Minnesota Medical Foundation, November 1940.*

The requirements for admission to the medical school have been revised extensively in recent years. In 1937 the executive faculty increased the amount of premedical work from two years to three, and the Admissions Committee undertook a program intended to insure the selection of students who, in addition to being capable scholastically, had shown evidence of good personality, character and adaptability to the study and practice of medicine.

To insure impartiality in interpreting premedical grades, a factor was evolved for each college which sends students to the medical school. It was computed by determining the average number of honor points per credit hour obtained in the medical school by a group of students from the college concerned. This figure was divided by the average number of honor points per credit hour earned by the same students in their premedical work. The factor ranges from 0.561 to 0.914 for various colleges. The honor point average of an applicant is multiplied by the factor for his college in determining his premedical grades. Thus inequalities due to a tendency of one college to give high grades and of another to be severe are equalized on the basis of actual performance in the medical school. Prior to this time applicants had been required to take the Moss and Minnesota medical aptitude tests to determine their ability to reason along lines thought to be necessary in the study and practice of medicine. To these were added the Strong Vocational Interest and Sophomore Culture tests.

The former is intended to indicate the fields in which the applicant's chief interests lie and the latter to assess his fund of general information. If serious deficiencies are uncovered by the latter test, the applicant may be advised to take more college work.

To learn something of the applicant's personality, "rating sheets" are sent to his high school principal, his family physician and the president of the college which he attended. If serious personality defects are suggested by these reports, or if sufficient data cannot be obtained, the applicant is called in for a personal interview with two members of the Admissions Committee.

Finally, the applicant must be examined at the University Health Service to make certain that he has no diseases which would make him unfit for the study of medicine.

This program has not been in effect long enough to determine whether it is resulting in the selection of better medical students and in the elimination of the unfit, since the first class so selected is now in its senior year. This class consisted originally of 107 members, of whom five dropped out permanently without failing and ten dropped out for a year while in good scholastic standing. Twenty-one (19.6 per cent) failed in the freshman comprehensive examinations, but fifteen passed on the second trial, while six were dropped from school for a second failure; 8.3 per cent failed in the sophomore comprehensives, all but one of these passing at the second trial; 5.2 per cent failed in the junior examinations. Seventy-five of the original 107 are now in the senior class. This is better than the average of 390 students taking each of these examinations in 1935, 1936 and 1937, in which the failures were 24, 15 and 13 per cent, respectively. Because of the small number of students admitted under the present régime, this is inconclusive though hopeful.

The freshman class of 1940-1941 consists of 114 members, 102 of them residents of Minnesota. Ten are women, five of them daughters of physicians; eighteen are physicians' sons. Forty-three had an average of B or better in their premedical work. The whole class had an average of 1.88 honor points per credit hour (B minus) in college.

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Dr. Edward Trudeau, ill with tuberculosis, went to the Adirondack Mountains in 1873 to spend his last days. He improved and became convinced that with rest and fresh air he had found a method of treatment of this disease. He established there what has become the famous Trudeau Sanatorium at Saranac Lake, N. Y., and so began the sanatorium treatment of tuberculosis in America.

## DO YOU KNOW WHAT PHYSICIAN—

1. Was the greatest philosopher of his day in England?

2. Was the first of the great American philosophers?

3. Is said to have been directly responsible for the surrender of Santiago de Cuba during the Spanish-American War, July 17, 1898?

*The answers are on page 352*

# Medical College News

*Medical schools, hospitals and individuals will confer a favor by sending to these headquarters original contributions, reviews and news items for consideration for publication in the Student Section.*

### A Medical Student at Seventy

Henry Franklin Cutler was born in 1862 in Greenwich, Mass. He graduated from Amherst College, took postgraduate work in Paris, Geneva and Berlin and was instructor in languages at the State Normal School, Westchester, Pa., in 1889 and 1890. Then for nearly forty years he was principal of Mount Hermon Boys' School in Massachusetts. He retired at the age of 70 and started on a trip around the world, still imbued with his boyhood ambition to be a physician. In Paris, he decided to matriculate in a medical school. In July 1940, in his seventy-ninth year, according to the Mount Hermon Alumni News, the University of Vienna officially announced that he was "promoted to the degree of Doctor of Medicine . . . at noon in the hall of the university." Mount Hermon Boys' School plans to have Dr. and Mrs. Cutler as their guests of honor next June when the school celebrates its sixtieth birthday.

### Scholarships for Tufts Freshmen

The Charles Hayden Foundation has awarded a grant of $10,000 to Tufts College Medical School, Boston, to be used for scholarships for selected members of the entering class next fall. Following the regular plan of the Charles Hayden Memorial Scholarships in other institutions, a portion of this will be used for outright scholarships during the first year of medical study. The remainder will be held as a special loan fund to be used in upper class years by those who held Hayden scholarships during the first year. Dr. Leonard Carmichael, president of Tufts College, in announcing the gift hailed it as a definite benefit to able and worthy young men who might otherwise be debarred from entering the medical profession. Dr. Cadis Phipps, professor of medicine at Tufts College Medical School, will serve as chairman of the committee administering the scholarship grants.

### Outpatient Department Banquets

Eight years ago Dr. Connie M. Guion originated at the old New York Hospital at Cornell University Medical College, New York, monthly outpatient department banquets at which some practical medical topic was to be discussed by a guest speaker and following which the lecture was to be open for discussion. At the December outpatient department banquet, the address was given by Dr. Soma Weiss, physician in chief of the Peter Bent Brigham Hospital, Boston, and professor of medicine at Harvard Medical School. Dr. Weiss's subject was "Spells of Unconsciousness in Medical and Surgical Practice," and as he graduated from Cornell in 1923 many of his former colleagues were in the audience. The paper was discussed by Dr. Harold G. Wolff of the department of medicine of Cornell and by Dr. William Andrus, who referred to its surgical implications, and by Joseph Hinsey, Ph.D., professor of anatomy.

### The Hamman Society at Western Reserve

At the meeting of the Hamman Society of the present school year, Oct. 14, 1940, Western Reserve University Medical School, Cleveland, Elmore R. McNeal '41 presented a paper on the diagnostic value of spinal fluid, and Paul F. Cooper '41 presented a case for diagnosis which was discussed by Edward S. Humel '41. At the November 11 meeting the program consisted of a debate between Austin S. Weisberger '41 and Walter A. Hoyt Jr. '41 on sulfapyridine versus sulfathiazole in the treatment of lobar pneumonia. Charles W. Stertzbach '41 presented a surgical diagnostic problem. The president of the Hamman Society for this year is John C. Cutler '41, the vice president Paul F. Cooper '41 and the secretary-treasurer Elmore R. McNeal '41.

### Noontime Radio Concerts at Illinois

A year ago the *Illini Scope* presented to the University of Illinois School of Medicine in Chicago a radio with which to provide noontime concerts given in room 106 for the purpose of recreation and enjoyment by the students. The interest of these periods has grown and through the efforts of William H. Welker, Ph.D., and Tom S. Jones, the well known medical artist, a new radio-phonograph has been presented to the school by the medical faculty. This instrument offers superlative reproduction. Daily notices of the programs for these concerts are posted on the bulletin board.

### Mrs. Joseph Goldberger Addresses Texas Students

Mrs. Joseph Goldberger addressed the students of the University of Texas Faculty of Medicine, Galveston, Dec. 19, 1940 on the subject "The Adventurous Dr. Goldberger," her husband, who won fame for research on the cause and prevention of pellagra. Mrs. Goldberger was a valuable assistant to her husband in his scientific experiments. Our correspondent writes that on the occasion of this address her cheerful personality and delightful informality won the praise of the entire school. Other guests who addressed the students recently were Dr. George M. Piersol, professor of medicine of the Graduate School of Medicine, University of Pennsylvania; Dr. Harvey B. Stone, associate professor of surgery, Johns Hopkins University School of Medicine, Baltimore, and Dr. Milton B. Cohen, director of the Hay Fever and Allergy Foundation, Cleveland.

### Woman's Medical College

Dr. Chevalier Jackson, president of the Woman's Medical College, Philadelphia, introduced the newly appointed acting dean, Dr. Margaret D. Craighill, at the opening of the ninety-first annual session of the college, September 18. Dr. Francis R. Packard gave an address on "The Colonial Hospital." The enrolment at the school is 115 students, including forty-one in the freshman class.

The following students were awarded scholarships:

*First Year:*
Dorothy Macy
Caroline Butchko
Leonore Alina J. R. Bajda
Margaret June Reed
Johanna Elizabeth Lund

*Second Year:*
Grace Rebecca Nachod
Sister Barbara Taggart

*Third Year:*
Judith Dudley Smith
Louise Mildred Dantuono
Eleanor Anne Soltau
Helen Teresa Metz

*Fourth Year:*
Badona L. Levinson
Dorothy May Brand
Katharine R. Guest
Beatrice Pearlstine
Jane Marshall Leibfried

Dr. Emily Dunning Barringer, president-elect of the American Medical Women's Association and now the only woman member of the House of Delegates of the American Medical Association, addressed the junior class of Woman's Medical College of Pennsylvania

at Philadelphia, November 15, on "The Modern Treatment of Gonorrhea." At the observation of Pan American Health Day, December 2, Dr. Damaso de Rivas, assistant professor of parasitology at the University of Pennsylvania, addressed the students on malaria control, and five students from Puerto Rico and the Canal Zone gave brief talks on local health problems in their countries.

### Christmas Party at Oklahoma

The fourth annual Christmas party at the University of Oklahoma School of Medicine, Oklahoma City, was held in the auditorium of the school, December 19, with the entire student body present. The arrangements were under the direction of the junior class, with Mr. Henry J. Freede as chairman. The various classes provided a program of music and other entertainment. The Christmas tree and trimmings were later given to the State University and Crippled Children's Hospital.

### Joint Meeting at Loyola

The Volini Medical Society, the Moorhead Surgical Seminar and the Lambda Rho Roentgenologic Society of Loyola University School of Medicine, Chicago, met in joint session November 28. Two senior students presented papers: James O'Neil on "Technics of Direct Blood Transfusions" and Matthew Boylan Jr. on "Technics of Indirect Blood Transfusions." Movies illustrating methods of transfusion were shown. The secretary announced the appointment of Dr. Herman F. De Feo as moderator of the Volini Society to succeed Dr. Gertrude M. Engbring.

### New Buildings at University of Kansas

A new four story clinic building costing $225,000 and containing eighty-five examining and demonstration rooms, an auditorium seating 300 persons and a kitchen to supply the University of Kansas Hospitals has been occupied at the University of Kansas School of Medicine, Kansas City. This building furnishes about three times as much space as the old dispensary, which is being removed from the campus, and along with the Children's Hospital, the Hixon Laboratory for Medical Research and the ward for Negro patients, all opened in the last two years, comprises a plant costing about $2,000,000.

### Student Research Club at Illinois

At the first meeting of the year of the Student Research Club, the present status of sulfathiazole was discussed. The club meets every second Friday at 2:30 p. m. Its object is to stimulate student research, to suggest problems of importance, and to aid in the distribution and coordination of equipment. The president of the Student Research Club this year is Robert L. Grissom '41 and the faculty adviser is Dr. George E. Wakerlin.

### Recreation Program at Georgia

One feature of the student recreation program at the University of Georgia School of Medicine, Augusta, is an informal concert of classical and semiclassical music played at various times between classes in the college auditorium, arranged through the efforts of Dr. Everett S. Sanderson of the department of bacteriology and public health. The recreation program is sponsored by the dean, Dr. G. Lombard Kelly. Three of these concerts have been held. The junior class for the last several Tuesday evenings has sponsored a series of movies demonstrating obstetric technic and procedures. Almost the entire student body has attended these movies. The local chapter of Alpha Kappa Kappa fraternity entertained the majority of the student body and many of the faculty members at a Christmas dance, Dec. 20, 1940.

### The Cook County Intern Examination

The results of the recent Cook County Hospital intern examinations showed, according to the *Illini Scope*, December, 1940, that the highest average grade (89.896) was that of Burton J. Soboroff, a Northwestern student; the second highest average was that of Jerome Solomon of Illinois, with an average of 88.9, and the third was Esther Pizer of Illinois, with an average of 88.396.

### Grand Presiding Senior Emeritus

Dr. Irvin Abell, of Louisville, Ky., now chairman of the Committee on Medical Preparedness of the American Medical Association, was presented with a diamond pin and received the title of Grand Presiding Senior Emeritus during the annual meeting of the Phi Chi medical fraternity at Louisville, Dec. 26-28, 1940. Among the other distinguished guests on the program were Dr. Eben J. Carey, dean of Marquette University School of Medicine, Milwaukee, and editor of the *Phi Chi Quarterly*, and Dr. Albert F. Saunders, of Valdosta, Ga.

### Symposium on Tuberculosis

The chapter of Alpha Kappa Kappa at Long Island College of Medicine, Brooklyn, sponsored a symposium on pulmonary tuberculosis, November 28, to which all students of the college, the faculty and members of the hospital staff were invited. The speakers were Dr. Elberton J. Tiffany, assistant professor of bacteriology; Dr. Alfred P. Ingegno, instructor in medicine, who discussed tuberculosis as it affects nurses and medical students; Dr. Emanuel Mendelson, assistant clinical professor of radiology; Dr. Tasker Howard, professor of medicine, and Dr. Lee D. Van Antwerp, of Undercliff, Meriden State Tuberculosis Sanatorium, Meriden, Conn. A moving picture entitled "First Stage Thoracoplasty" was shown, and after the meeting refreshments were served at Donnellon House.

### New A. O. A. Chapter at Medical College of Virginia

The Brown-Séquard Society, honor medical organization at the Medical College of Virginia, was formally made a chapter of the national honor medical society, Alpha Omega Alpha, at appropriate ceremonies December 4, at which Dr. Walter L. Bierring, national president of the fraternity, conferred the charter on the local group. The Brown-Séquard Society was organized at the Medical College of Virginia in 1931 and A. O. A. was organized at the University of Illinois College of Medicine, Chicago, in 1902. This national honorary society, which has chapters in many medical schools, seeks to promote scholarships and to encourage high standards among medical students and graduates. Dr. Josiah J. Moore, Chicago, national secretary of A. O. A., presented keys and certificates to the following local chapter members: Dr. Frank L. Apperly, professor of pathology; Dr. Claude C. Coleman, professor of neurosurgery; Dr. Harvey B. Haag, professor of pharmacology; Dr. W. B. Porter, professor of medicine; Dr. Lee E. Sutton Jr., professor of clinical obstetrics, and the following senior students: Herbert C. Allen Jr. '41 of Richmond; William E. Daner '41 of Paden City, W. Va.; George A. Stewart Jr. '41 of Norfolk, and Adney K. Sutphin '41 of Beckley, W. Va.

W. T. Sanger, L.L.D., president of the college, presided at the ceremonies. Dr. Sutton, the dean, accepted a charter on behalf of the school and Dr. Porter gave an

address. The banquet was attended by Major General Merritte W. Ireland, U. S. Army, retired, former surgeon general of the Army and president of the National Board of Medical Examiners; Dr. Hugh S. Cummings, former surgeon general of the U. S. Public Health Service and now director of the Pan American Sanitary Bureau, Washington, D. C.; Dr. Hugh H. Trout, Roanoke, surgeon and past president of the Medical Society of Virginia; Dr. J. Shelton Horsley, Richmond; Dr. Harvey E. Jordan, dean, University of Virginia Medical School, and many others.

### Wisconsin State Board Questions

The following questions were given by the Wisconsin State Board of Examiners at the examination in Milwaukee, June 24, 1940:

OBSTETRICS AND GYNECOLOGY

1. Give signs of separation of the placenta in the third stage of labor.
2. How is postpartum hemorrhage prevented? How treated?
3. Discuss and give treatment of nausea and vomiting in early pregnancy.
4. Describe measures employed in the treatment of ruptured ectopic pregnancy.
5. Give your advice to a woman (three) months pregnant concerning her diet so that she will have ample mineral requirements for herself and fetus.
6. Discuss the management of frank breech presentation during the first stage, second stage. In what position is the patient always placed for breech delivery?
7-8. Give theories on the etiology of eclampsia, chief pathologic findings and method of treatment. What determines your advice to the patient concerning subsequent pregnancies?
9. Discuss the sphere of value of x-rays, radium and surgery in cancer of the cervix, fundus and ovary.
10. Describe briefly the phases through which the endometrium passes in one menstrual cycle.
11. How would you treat (1) cervical polyp (2) urethral caruncle?
12. Discuss the role of cauterization of the cervix in the prevention of cancer.

### Transylvania University

THE JOURNAL, Nov. 30, 1940, page 1944, stated that Dr. Thomas H. Chivers graduated "from Transylvania University (now the University of Kentucky) in 1830," which statement, Dr. D. P. Hall of Louisville writes, is partially incorrect. Transylvania University is not now the University of Kentucky; the lineal descendant of the medical department of Transylvania University is now the School of Medicine of the University of Louisville. Transylvania University is located at Lexington, Ky.; at one time, for a few years, it assumed the title Kentucky University, but it was never the University of Kentucky (the present state institution).

### New Sorority at Tennessee

The twenty-first chapter of Alpha Epsilon Iota, national women's medical sorority, was installed as the Omega Chapter at the University of Tennessee College of Medicine, Memphis, Sept. 28, 1940, with Dr. Mary Morris of St. Louis officiating. The new chapter had twelve charter members, all students except three who were alumni. Vera Lee Stewart was elected president of the sorority.

### Louisiana's New Journal

Louisiana State University School of Medicine, New Orleans, has just published the first issue of the *Journal of the Louisiana State University School of Medicine,* which it is assumed is to replace the weekly newspaper known as the *Tiger.* Laurence B. Weiss '41 and Thomas R. Wilson '41 are co-editors of the new journal; Walter A. Salatich '42 is associate editor; Thomas M. Durham '43 is business manager. On the editorial board are three members of the faculty in addition to the following students: Frank A. Cain '41 chairman; Burdette E. Trichel '41, Joe C. Much '42, George A. Degenshein '42 and Alvin F. St. Amant '43. The first issue contains scientific articles and interesting editorials and news items.

### Virginia

The University of Virginia Department of Medicine, Charlottesville, recently announced the founding of a scholarship on bequest of the late Dr. James L. Minor, ophthalmologist, of Memphis, Tenn.

The first annual Phi Beta Pi Lecture at the University of Virginia Department of Medicine was given, October 14, by Dr. James B. Murphy of the Rockefeller Institute for Medical Research, New York, on "The Present Status of Cancer."

### New Student Publication

*Tufts Medical Journal,* a new periodical published by the students of Tufts College Medical School, Boston, began publication in November. The first issue had 32 pages.

### "DO YOU KNOW WHAT PHYSICIAN"

Following are answers to the questions appearing on page 349.

1. John Locke, who after a thorough preliminary education, entered Oxford, receiving his degree in medicine in 1666. He immediately entered medical practice. Later, in 1672, he was made secretary of the Board of Trade under Lord Shaftesbury, a position which he held with great distinction until 1675. Then he went to France, where at Montpellier and Paris he began work on his great contribution to philosophy, his Essay Concerning Human Understanding, which was published in 1690. In the same year he published "An Essay on Civil Government," which has been considered by some authorities as the most important contribution ever made to English constitutional law by an author who was not a lawyer by profession. Dr. Locke died in 1704.

2. William James, who was born in New York City in 1842 and graduated from Harvard Medical School in 1869. He was instructor and later assistant professor of anatomy and physiology at Harvard from 1872 to 1881, and in the latter year became professor of philosophy at Harvard, a position which he held until 1907. Among his writings were "The Will to Believe," "The Meaning of Truth," "Varieties of Religious Experience," "Essays in Radical Empiricism," "Some Principles of Philosophy" and "Pluralistic Universe." His philosophy was typically American. Dr. James died in 1910, the foremost philosopher and psychologist of his day.

3. Dr. George E. Goodfellow, who was born in Sierra County, Calif., Dec. 23, 1855. Dr. Goodfellow received his degree in medicine from the University of Wooster. He practiced medicine for a while, then entered the army as an acting assistant surgeon. He again returned to civil life and practiced medicine in Tombstone, Ariz., and again joined the army at the outbreak of the Spanish-American War, in which he served with distinction. After the battle of San Juan and El Caney, blindfolded and under a flag of truce, he was led into a Spanish camp, making several such trips, the final outcome of which was the surrender of the Spanish general. After the war Dr. Goodfellow returned to private practice in San Francisco, specializing in urology. Later he became chief surgeon of the Southern Pacific Railroad in Mexico and left San Francisco. He died in Los Angeles in 1910.

# Book Notices

**Hearing and Equilibrium.** By H. Macnaughton-Jones, M.B., B.Ch., B.A.O., Clinical Assistant, Ear and Throat Department, North London Hospital, London. Cloth. Price, $2.50. Pp. 128, with 48 illustrations. Baltimore: William Wood & Company, 1940.

This treatise on the physics and the physiology of the ear is a welcome contribution to our literature. It is couched in terms which make comprehensible obtuse mathematical language to the otologist. It clarifies the working of natural laws in physics and explains phenomena difficult to visualize. It renews interest in how we hear and how we maintain balance or equilibrium.

The author's approach to the problems concerned is somewhat revolutionary and, as he expects, will be met with opposition. Time for study and consideration of the ideas the author advances will have to elapse before his views and presently held theories and principles are reconciled. The new concepts he advances too will engage serious study. At least here is presented a fresh outlook on problems with which otology is preoccupied.

The author sets out to prove that the configuration of the external auditory canal, the structure of the membrana tympani and the anatomy of the inner tympanic wall are so designed for the purpose of directing sound waves to the round window where they are received. The movements of the ossicular chain are given as a protective function. Their movements are clearly defined and illustrated. Their function of protection is designed to dampen excessive strain on the basilar membrane. This is accomplished through the muscles attached to the ossicles. Sound waves, transmitted to the fluids in the cochlea, produce a movement of the basilar membrane, which has a recoil force which lasts a specified time in each segment. This is understandable from the anatomic variations in the length of the basilar membrane in the cochlea as a whole. The author also presents intriguing explanations of the functions of the tectorial membrane and gives reason for the division of the scala tympani by Reissner's membrane, the function of the spiral septum and the mechanics of Corti's organ.

In themselves, the detailed studies and observations of the semicircular canals in their role for the maintenance of equilibrium are recommended to otologic students for serious consideration. They are worth while.

All portions of this monograph are freely illustrated with descriptive diagrams and other illustrations. These simplify both the physical and the engineering principles involved in the author's presentation of his conception of a moot physiologic problem.

In view of the renewed interest of the otologic surgeon toward seeking a surgical remedy for deafness, the ideas and conceptions presented in this volume furnish a new basis on which to evaluate the acoustic function. It may seem trite to say that the book must be read for appreciation of a new concept of the acoustic function, but the reviewer knows no other manner of emphasizing the importance he places on this little volume than to suggest that it be printed in its entirety in one of our current otologic publications. It should be in the hands of every student and practitioner of otology.

The reasoning is sound and logical. For the clinician, however, many aspects of the problem of how we hear and how we maintain our equilibrium are still unsettled.

**Starost: Trudy konferentsii po probleme geneza starosti i profilaktiki prezhdevremennogo stareniya organizma, Kiev, 17-19 Dekabrya 1938g.** [Old Age: Reports of Conference on Problems of Genesis of Old Age and Prophylaxis of Premature Senescence of Organism.] Paper. Price, 22 rubles, 50 kopecks. Pp. 490, with illustrations. Kiev: Izdatelstvo Akademii Nauk USSR, 1939.

This large volume contains papers which were presented at the conference on old age which was held in Kiev in December 1938 under the auspices of the Ukrainian Academy of Sciences and the Institute of Experimental Biology. Old age is a serious economic problem in Soviet Russia in view of the liberal provisions of the old age pension act and the social security legislation. The volume contains some fifty papers dealing with various aspects of old age. There is a series of papers on the changes of the various tissues, organs and systems of the bodies due to old age with several excellent papers on changes in the central nervous system. The main value of the volume consists of the report of an exhaustive study of a group of 33 old persons between the ages of 90 and 142 years of age. The oldest people of Russia are found in Central Caucasus, and a separate expedition was sent there to study this group of the aged. Careful and painstaking studies were made of their metabolism and general physiology, with special stress on neuropsychiatric studies. In view of the tendency of the old people to exaggerate their age, careful attempts were made to check the age by matching it with certain historical events in the turbulent history of Caucasus. There was nothing unusual about the metabolism of these people which was different from any other group of old people. On the other hand, they all demonstrated an unusual stability of the nervous system with a history of extreme moderation and even frugality in all their habits from an early age, especially in the field of sexual activity. The volume abounds in many curious and interesting observations. In spite of the great mass of physiologic and metabolic studies, there is but little original in them. Throughout the volume there is a definite optimistic note in reference to old age, and the fact that we do not appreciate sufficiently the capacity of elderly persons in various occupations. A study of performance of older men in industry showed their extreme value for all sorts of skilled, technical occupations and especially in maintenance jobs which are vital in modern industrial plants. In connection with these studies, provisions were made in legislation to stop the granting of pensions at a certain fixed age. The old age is an elastic concept, and old age pensions should be granted only when persons are not able to work any more irrespective of the chronologic age. There is quite a good deal of feeling that old age as we see it at the present time is largely the result of some sort of intoxications and that the normal man in a normal environment should not get old until he is 150 years of age. The evenings of the meetings were devoted to general discussion with a stenographic account of the various opinions presented. There is an excellent bibliography of 855 references in which modern American authors are well represented.

**The 1940 Year Book of Public Health.** Edited by J. C. Geiger, M.D., Dr.P.H., Director of Public Health, City and County of San Francisco. Cloth. Price, $3. Pp. 560. Chicago: Year Book Publishers, Inc., 1940.

Dr. J. C. Geiger, editor of this yearbook, has wisely selected abstracts from great numbers of publications and makes personal comment on almost every one of the abstracts of importance. The book covers every section of interest in modern public health. There is special emphasis on industrial hygiene, as well as discussions of borderline topics like health education, child hygiene and mental hygiene. The book is highly suggestive and the 296 editorial remarks are a fine commentary on modern ideas in public health.

**Clinical Electrocardiography.** By David Scherf, M.D., and Linn J. Boyd, M.D., F.A.C.P., Associate Clinical Professor of Medicine and Professor of Medicine, The New York Medical College, Flower and Fifth Avenue Hospitals, New York. Cloth. Price, $6.25. Pp. 362, with 207 illustrations. St. Louis: C. V. Mosby Company, 1940.

This book of electrocardiography, according to the authors, is "not designed primarily for those beginning their study in this field." The text includes the usual material concerned with the normal electrocardiogram and various physiologic variations, the arrhythmias and disturbances of stimulus formation and conduction. The authors' discussions of the subjects of interference dissociation and parasystole and the bundle of Kent deserve especial commendation. The recent advances in the use of lead 4 are well analyzed and the point is made that "the value of chest leads is often exaggerated." Adversely, comment might be made regarding the reproduction of the details of the illustrative electrocardiograms. The authors also do not follow the terminology of that advocated by the American Heart Association. There is comparatively little discussion of the effect of drugs on the electrocardiogram. One might well disagree with the authors on the interpretation of the electrocardiogram with reference to endocrine disturbances. For example, "In some cases of ovarian insufficiency . . . distinct changes in the terminal deflection of the electrocardiogram are frequently found." The text has an extensive bibliography and is well indexed.

**Office Urology With a Section on Cystoscopy.** By P. S. Pelouze, M.D., Assistant Professor of Urology, University of Pennsylvania, Philadelphia. Cloth. Price, $10. Pp. 766, with 443 illustrations. Philadelphia & London: W. B. Saunders Company, 1940.

In giving his reason for the presentation of this book, the author states that he has attempted to comply with the request of the publisher to write a book on his experience in office urologic diagnosis and treatment. "One cannot spend years at office urology without feeling that there are many operations performed that rather easily might have been avoided by early attention to little things. It is of these little things that I have tried to write. . . ." Again, "there is little need that a book of this type be made a repository for medical curiosities. If there is a need, it is for the portrayal of the things that doctors see and treat in their daily experiences, and it is to these that the book is devoted." When the author sticks to his concept of the mandate, he makes his book exceptionally lucid, informative and authoritative. When the book goes beyond the self-imposed *raison d'être* and includes major surgical urology and rare urologic conditions that are obviously not in the category of office urology, it flattens somewhat. The arrangement of the subject matter begins logically with office setup and covers urologic anatomy, physiology, history taking, examinations, diagnoses, symptoms, treatment and diseases of the urogenital system. It contains a well written discussion of the sexual problems and an exceptionally good chapter on cystoscopy, its technic and interpretation of observations. One has the feeling that, if books on the other specialties were as well conceived and handled, a careful perusal of them would perforce enhance the efficiency of the physician in his general practice.

**Operative Surgery.** By J. Shelton Horsley, M.D., LL.D., F.A.C.S., Attending Surgeon, St. Elizabeth's Hospital, Richmond, Va., and Isaac A. Bigger, M.D., Professor of Surgery, Medical College of Virginia, Richmond. With Contributions by C. C. Coleman, M.D., F.A.C.S., Professor of Neurological Surgery, Medical College of Virginia, Austin I. Dodson, M.D., F.A.C.S., Professor of Urology, Medical College of Virginia, John S. Horsley, Jr., M.D., Associate Professor of Surgery, Medical College of Virginia, and Donald M. Faulkner, M.D., Associate Professor of Orthopedic Surgery, Medical College of Virginia. Volumes I and II. Fifth edition. Cloth. Price, $18 per set. Pp. 768; 769-1567, with 1,391 illustrations by Helen Lorraine. St. Louis: C. V. Mosby Company, 1940.

These two volumes represent an interesting development of modern surgery. Those who have the opportunity should read the prefaces of all five editions, which are presented at the beginning of volume I. At first almost entirely the work of the senior author, the work, because of the rapid growth of modern surgery, forced not only new editions but also the addition of several collaborators. At present it is difficult to evaluate the importance of such contributions to surgical literature. They do respond to a definite demand, and in spite of increasing specialization of surgeons the general surgeon, like the general practitioner, is likely to be with us for some time. The material is not encyclopedic in character, but a number of operations for various disorders are usually presented. The technic of the operations is couched in clear language and a number of good illustrations fortify the text. One of the more pleasing points is the frequent indication by the author of the method he prefers and why he prefers it. The first volume is devoted to general principles and surgery of the head, neck and thoracic regions, as well as orthopedic and plastic surgery. The second includes the remainder of the alimentary tract, the abdominal wall and neurosurgery. The urogenital system also is discussed in this volume. The comprehensive scope of the work, its compact nature and its avoidance of encumbering and obsolete operative technics enhance the value of this work to general practitioners and surgeons alike.

**Diseases of Workers.** The Latin Text of De Morbis Artificum [by] Bernardini Ramazzini, 1713, revised, with translations and notes by Wilmer Cave Wright. The History of Medicine Series issued under the auspices of the Library of the New York Academy of Medicine, Number 7. Cloth. Price, $5. Pp. 549, with 3 illustrations. Chicago: University of Chicago Press, 1940.

Bernardino Ramazzini (1633-1714), professor of the theory of medicine at Modena and of practical medicine at Padua, is distinguished as the author of the first important treatise on occupational diseases. Readers of this excellent translation will find his work comprehensive, solicitous for the welfare even of cleaners of privies and cesspits, keen in the search for the physical causes of the afflictions of workmen, and alert to suggest methods of prevention. He evidently was a good observer and an excellent judge of human kind; witness the pungent remark concerning farmers: "It follows that in my opinion men of this class should be treated by the direct and summary method; any other that is roundabout and calls for an outfit of various sorts gradually consumes the strength of these peasant folk: 'Who seeks to cure but makes it worse.'" Mrs. Wright, who translated the De contagione of Fracastorius, is professor emeritus of Greek in Bryn Mawr. She brings to this task a familiarity with the classics and Italian medicine of the seventeenth century. Her introduction reviews the life of this great scholar, and her critical bibliography and extensive notes illumine the translation and enlarge the picture of medical practice in the days of Fracastorius and Ramazzini. Readers of her well wrought translation will enjoy not only this rather intimate picture of medical practice of the seventeenth century in Italian university cities but also the revelation of the then current medical controversies and the vivid and humorous picture of the social, business and industrial life in Italy from 1680 to 1713.

**Actas de la décima Conferencia sanitaria panamericana, Bogotá, septiembre 4-14, 1938.** Oficina sanitaria panamericana, publicación No. 136. Cloth. Pp. 941, with illustrations. Washington, D. C.: Pan American Sanitary Bureau, 1939.

This volume contains the general acts of the tenth Pan American Conference, held in Bogotá Sept. 4-14, 1938, and the articles on official topics on matters of public health and sanitation, with reports on the progress from the date of the ninth Pan American Sanitary Conference, which was held in Buenos Aires in 1938, up to now. The articles presented in the course of the sixteen different plenary sessions are concerned with epidemiology and prevention of yellow fever, pestilential diseases, infectious diseases transmitted by a virus and leprosy, international relations for sanitation in aviation and navigation, control of stupefactive drugs, venereal diseases, parasitic diseases, potability of water, rural sanitation, food, hygiene for mothers and infants, and eugenics. The articles of the extraordinary sessions are concerned with the history of malarial sanitation, especially related to the discovery of quinine, and memorial honors for workers in hygiene. The articles of the closing session are reports of executive work, motions and resolutions. The book ends with an appendix with reports of delegates and directors of public health of Pan American countries on the fulfilment of the resolutions adopted in the nine Pan American sanitary conferences. The book is presented to sanitary, hygienic and medical libraries with the compliments of the Pan American Sanitary Bureau of Washington, D. C.

**Essentials of the Diagnostic Examination.** By John B. Youmans, B.A., M.S., M.D., Associate Professor of Medicine and Director of Postgraduate Instruction, Vanderbilt University Medical School, Nashville. Fabrikoid. Price, $3. Pp. 417, with 36 illustrations. New York: Commonwealth Fund; London: Oxford University Press, 1940.

This is a dapper little volume, well printed on thin paper and of such size, shape and weight as to fit conveniently into one's pocket or bag. It is unpretentious. The essentials of the diagnostic examination are described, history taking in sixteen pages, physical examination in 142 pages and laboratory tests in the remaining 218 pages. On first sight this spacing of the material may appear unusual and as if undue emphasis was placed on the laboratory and too little on history taking. Such is not the case. One cannot tell how to take a good history beyond suggesting bare outlines. The technic of physical examination is easier to describe and certainly the author outlines the methods of physical examination in a satisfactory manner, including a common sense, easily understandable description of neurologic examination. The laboratory manual part of the book must have been the least interesting to write. It describes ordinary clinical laboratory work and methods with clarity and detail. On the whole, the new Diagnostic Examination is a good 1940 model. Every doctor ought to have an up-to-date booklet of this character as part of his standard equipment, in constant use and as well thumbed as any priest's book of prayers. This particular Diagnostic Examination contains few errors, is handy and, above all, is put together by a competent clinician thoroughly familiar with all of which he writes. It deserves a successful life.

# Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

## SULFANILAMIDE DERIVATIVES AND QUINIDINE FOR CYSTITIS AND CARDIAC FIBRILLATION

*To the Editor:*—**A patient with a severe chronic cystitis also has a cardiac fibrillation which was brought on by a toxic goiter. The goiter was removed several years ago but the cardiac fibrillation can be controlled only by quinidine treatment. The bladder symptoms improve temporarily by irrigating with boric acid solution and instillation of mild protein silver. Methenamine does not seem to help her much. The urologist after cystoscopic examination confirmed the diagnosis of chronic cystitis due to colon bacilli with laboratory evidence of a slight degree of infection in the right kidney pelvis. Would it be safe to give her some one of the sulfanilamide group, such as sulfathiazole, at the same time as she is taking the quinidine sulfate (8 grains, or 0.5 Gm., a day) and phenobarbital?**

**M.D., Illinois.**

ANSWER.—Sulfanilamide or its derivatives such as sulfapyridine or sulfathiazole should be administered with care to patients who are suffering from cardiac dysfunction. This is especially true if heart failure is present. It is probable that some form of mandelic acid should be tried before sulfonamide derivatives are used in this particular case. If this therapy did not bring about the desired results, one could use sulfathiazole, giving about 1 Gm. three times a day at 8 a. m., 2 p. m. and 8 p. m. Care should be taken that the urine output is maintained at least 1,000 cc. a day, and it also would be wise to determine whether or not impaired renal function is present. This can easily be accomplished by doing a phenolsulfonphthalein test. If this test shows impairment of renal function care must be taken, if sulfathiazole is prescribed, to prevent the drug from accumulating in the blood and tissues of the patient because, with decreased kidney function, sulfonamide drugs are not excreted in a normal fashion. As far as is known at the present time, the administration of quinidine sulfate and phenobarbital does not constitute contraindications for sulfonamide therapy.

## SOLDERING FLUID CONTAINING HYDROCHLORIC ACID, AND PULMONARY FIBROSIS

*To the Editor:*—**A patient who has been a tinsmith for about twenty years and has used muriatic acid freely in his work now has quite severe dyspnea and yet not many definite physical abnormalities to account for it except what seems to be a generalized fibrosis of the lungs as seen on the x-ray plate. Is it possible that the long continued use of this acid will cause such a change when no attempt is made to draw the fumes away from the workers? If so, will Spear soldering fluid, grade super, made by the Jordan Company, Chicago, do the same? He is going to the United States for care in the hope that he has a curable condition but we want to prevent the occurrence of a similar condition in his sons, who are doing the same work. They say this Spear fluid does not give off many fumes and is not so choking in its effect when breathed. If these fumes will cause a fibrosis, what can be done for patients when they reach this stage of disabling dyspnea? Is diathermy of any value?**

**David Hoehn, M.D., Fairbanks, Alaska.**

ANSWER.—The characteristic action of hydrochloric acid vapors leads to erosion of the teeth, extensive caries or the loss of teeth, together with acute episodes of conjunctivitis, pharyngitis, bronchitis with occasional pneumonia or minor pulmonary hemorrhage. Unless some or all of these manifestations now exist or have existed in the past, the present disabling dyspnea and fibrosis probably is not associated with hydrochloric acid as the cause. Koelsch (Ueber die Gesundheitsverhaltnisse der Arbeiter in der Saureindustrie: Referat erstattet für ein Gutachten des Reichsgesundheitsrats) cites the German records indicating that this class of workers are infrequently affected with tuberculosis but other respiratory diseases are more frequent than for other classes of chemical workers. Death rates among tinsmiths from all causes barely exceed the general average, and the causes of death do not include any characteristic occupational diseases.

It is not known that these hydrochloric acid vapors or the vapors from any other soldering fluid may occasion any pulmonary fibrosis distinctive of any special occupational disease. From long years of exposure to any respiratory irritant, chronic sinus involvement may be expected which will eventuate in heavier markings found in x-ray films of the lungs. It is reasonable to believe that twenty years of exposure to hydrochloric acid vapors might increase the amount of pulmonary fibrosis, but conversely there is no warrant to associate this noncharacteristic increased fibrosis with total disability, marked dyspnea or any other feature pointing to the hydrochloric acid as the direct and specific cause. If it may be assumed that the present dyspnea and disability are associated with the fibrosis, it is not known that any diminution of the fibrosis itself can be brought about through any treatment, including diathermy. On the other hand, thorough examination may reveal causes of the dyspnea unrelated to the fibrosis which may prove to be amenable to treatment.

Spear soldering fluid, manufactured by the Jordan Company, of Chicago, consists of zinc cut in hydrochloric acid, thus leading to zinc chloride. The manufacturer states that proper manipulation eventuates in a soldering fluid basic in nature and thus without any content of free hydrochloric acid. This manufacturer points out that impure zinc, if used, might lead to the presence of unwanted harmful metals, such as lead and arsenic. The claim is made that such impurities are eliminated in the Spear fluid. It is believed that this particular soldering fluid, like others, even though free from hydrochloric acid, still may constitute a skin irritant and its vapors an irritant to the conjunctivas and respiratory tract.

## PROBABLE TUBERCULOUS ARTHRITIS

*To the Editor:*—**A white woman aged 37, married, has had a firm swelling and somewhat stiffened left knee for one year. The condition began insidiously and has been treated as arthritis with no change. There is some fixation, and pain is precipitated by wide excursions. X-ray examination shows widening of the joint space on one side with haziness of part of the joint surface of the femur. Complete rest of the knee joint was brought about by a plaster cast to the leg for one month. The condition remains the same except that there is more fixation and more pain when walking and especially when climbing stairs. A physical examination at this time reveals no demonstrable pathologic condition. In the family history an older sister died of pulmonary tuberculosis. In childhood they were close and three years after the older sister left home she died of pulmonary tuberculosis (now fourteen years ago). The personal history brings out that the patient has enjoyed usual good health. She has been married for eight years. The first pregnancy terminated spontaneously at three months. The second pregnancy was a full term stillbirth and the third pregnancy resulted in a full term normal infant now 2½ years old. About three years ago in the winter she had a bad attack of "flu" (in her own words) from which she did not really recover. She then had many moist rales over the apexes, which persisted after cough with a temperature of 99.6 F., respirations 20 and pulse 104. I made a diagnosis of pulmonary tuberculosis. The next day the chest was roentgenographed and the report is that there is no evidence of tuberculosis but extensive bronchitis. Under treatment the cough gradually subsided and the patient gained weight. She later went through a normal and uneventful pregnancy and now has a child 2½ years old. She enjoyed apparent good health until one year ago, when the knee began to swell and hurt. The knee now remains apparently the same size as at onset. The joint has been at rest four weeks and the leg is back in the cast for an additional four weeks. Will a diseased joint like this come back to useful function if fixed too long? A synovectomy is proposed if fixation fails. After the synovial membrane is removed, where will the joint fluid come from so that the joint will function normally? There is some fluid in the joint that could be used in a guinea pig. Is the guinea pig test reliable and accepted now as an indisputable fact of diagnosis of tuberculosis? I have heard that some pathologists put little stock in the test for they say that guinea pigs frequently die of tuberculosis even without being inoculated with tuberculous material. Incidentally, shortly after the chest x-ray films were made a purified protein derivative second strength test was made on her and the reading is recorded as definitely positive.**

**M.D., Ohio.**

ANSWER.—The history of a monarticular progressive arthritis which has failed to yield to conservative treatment is suggestive of tuberculosis of the joint. The haziness of the joint space and of the bones as shown in the x-ray film and also the family history and past history of the patient lend further evidence in favor of this diagnosis. The patient should have the knee joint aspirated and the fluid injected into a guinea pig. Guinea pig inoculation is a reliable test for tuberculosis when it is positive. A negative test does not necessarily mean that the patient does not have tuberculosis. It is advisable that two guinea pigs be injected in case one should die before sufficient time has elapsed for the disease to become manifest. If the guinea pig test is positive, arthrodesis of the joint might be advisable, as it is doubtful that recovery from tuberculosis will occur in an adult as long as there is movement in the joint. If the guinea pig test is negative and the patient continues to be disabled and the joint does not yield to conservative treatment, a biopsy and probably an arthrodesis are indicated even if definite tuberculosis cannot be proved, as this seems to be a progressive destructive lesion.

## ABDOMINAL PAIN AND VASCULAR FAILURE

*To the Editor:*—A young woman complained of a vague abdominal pain associated with nausea, subnormal temperature, pulse and respiratory rate, low blood pressure and excessive weakness. There was only slight tenderness in the right lower quadrant with almost no rigidity. The past history was negative. On admission to the local hospital a blood study revealed a total white count of 22,800 with a differential count of 93 per cent polymorphonuclears and 7 per cent lymphocytes. No abnormal cells were seen. The red blood count and hemoglobin were apparently normal. The white cell count was repeated six hours later and it was seen to have dropped to 16,200. The following morning the count was 14,600 and prior to discharge the next day it was 12,700 with 64 per cent polymorphonuclears, 32 per cent lymphocytes and 4 per cent eosinophils. While at the hospital the patient rallied almost immediately with intravenous saline solution and stimulative therapy; the abdominal pain disappeared spontaneously, as did the tenderness. Because of recurrent furuncles I have been giving the patient a course of Staphylococcus aureus vaccine, using graduated doses, every three days. The last dose, which was 10 minims (0.6 cc.), was given two days prior to the onset of the present complaint. At no time, however, has there been any evidence of hypersensitiveness to the vaccine. 1. Could a minute perforation in the appendix being sealed off immediately by the omentum be a possible cause of such a clinical picture? 2. Could the vaccine contribute to the elevated white cell count in the face of such a toxic shock? 3. Is there any chance of the picture being allergic in nature, because of the eosinophils which had not appeared in the three earlier counts?

Sigmund J. Posner, M.D., Ludlow, Mass.

ANSWER.—It is difficult, if not impossible, to explain accurately what happened in this case. The symptoms of subnormal temperature, pulse and respiratory rate together with low blood pressure and excessive weakness resemble those seen in peripheral circulatory failure. The rapid response of the patient to stimulative treatment and the intravenous infusion of physiologic solution of sodium chloride is quite consistent with such a picture. Peripheral circulatory failure may be caused by the rupture of an acutely inflamed appendix. The initial leukocyte count is quite in keeping with an acute appendicitis and yet it is most unusual, but not impossible, for an acutely inflamed appendix to rupture with only "vague abdominal pain." Just preceding and at the time of the rupture one expects rather sharp pain, which is relieved by the rupture.

A simple acute gastro-enteritis could be responsible for the symptoms, including the blood count, described.

An allergic response is capable of producing peripheral vascular failure but there are many objections to a diagnosis of anaphylactic shock in this case. Anaphylactic shock seldom waits two days to make its appearance. Except in foreign protein shock, which this was not, the leukocyte count does not rise above 20,000. Four per cent of eosinophils with a total white count of 12,700 cannot be called a true eosinophilia. The eosinophils must rise above 600 per cubic millimeter before such a diagnosis can be made. In this case there were 508. It seems unlikely that the vaccine was involved in any way.

The absence of eosinophils in the really high white counts is not unusual. The eosinophils frequently disappear from the circulating blood with a sudden upsurge of the neutrophils. Reappearance of the eosinophils is considered an omen that the cause of the neutrophilia is subsiding.

## YEASTS IN URINE AND PROSTATE

*To the Editor:*—A woman of about 55 has been complaining of some urinary disturbance for the past year. Catheterized specimens and stained smears of the sediment with Gram stain reveal in every instance mycelia and large quantities of pus. I have tried various forms of treatment, including irrigations, and sulfanilamide, with no measure of success. A man aged 30 had a gonorrheal infection about two years ago and now has a large boggy prostate. Cultures taken from the prostatic secretion after massage show yeast cells in large numbers. I would appreciate any suggestions as to the treatment in these two cases.

B. B. Coker, M.D., Durant, Okla.

ANSWER.—Yeasts are rarely found in the vesical urine. Their occurrence in the prostatic secretion is even more rare. They are usually considered as saprophytes, and whether or not they occur as true pathogens in the prostate and bladder is open to question.

Bladder instillations of 30 cc. (1 ounce) of gentian violet, 1:1,500 solution, two or three times weekly are often effective in eliminating yeast from the urine. Any associated bacterial infection should be treated with the chemotherapeutic agents most effective for that particular organism, including the sulfanilamide compounds and mandelic acid. In the woman the search for yeast infection in the vagina should be made and, if present, treatment should be instituted. Daily application of 1 to 2 per cent gentian violet is sometimes effective. In the man, when yeasts are found in the prostate deep urethral instillations of 1:1,500 genitan violet solution plus prostatic massage should be beneficial. Diabetes mellitus, if present, should be strictly controlled.

## KERATOCONUS AND PREGNANCY

*To the Editor:*—Will you please give me some information on the present status of the relationship of pregnancy to keratoconus. I am particularly interested to know whether or not pregnancy will aggravate the condition.

M.D., California.

ANSWER.—There are no specific cases reported in the literature of an increase in a keratoconus due to pregnancy. But there is a widespread opinion among those familiar with the condition that an endocrine disturbance plays a great part in the causation and progress. For instance, Duke-Elder (Textbook of Ophthalmology, vol. 2, p. 2028) said "It is generally admitted that the ductless glands exercise a very potent influence over growth processes and it would not be surprising that an upset of their balance should alter the condition of a tissue which is primarily supportive, a view borne out by its usual incidence about the time of puberty and its preference for females." Two pages later he said "The endocrine system should be minutely overhauled and any imbalance looked into, especial attention being paid to early menstrual disturbances in girls: thyroid and female sex hormones may be indicated." With these factors in mind, it would not be surprising if pregnancy would exert a more or less deleterious influence on keratoconus. But there is no specific evidence to support that statement.

## TREATMENT OF TRICHOCEPHALUS TRICHIURIS

*To the Editor:*—Please outline treatment for Trichocephalus trichiuris infection in a 9 months old infant. Repeated treatments with hexylresorcinol in 1½ grain doses given over a period of two months and at two week intervals have been ineffective.

Beulah M. Kittrell, M.D., Maryville, Tenn.

ANSWER.—The treatment of Trichocephalus trichiuris infection is at the present time unsatisfactory. Hexylresorcinol has been found about as effective as any other drug in this condition, but it has been impossible to clear up any high percentage of cases even with this drug. The only thing that is known in which real success has been reported is the treatment with the sap of the fig tree. The active principle of this sap has been shown to be a proteolytic enzyme which digests the worm. Although the natives have used this for generations in the treatment of worms, this substance cannot be recommended for treatment in human beings at present, as it is known that it can digest the intestinal tract if the mucosa is sufficiently irritated. It has no effect whatever on the normal intestinal tract.

## OINTMENT BASE FOR SULFANILAMIDE

*To the Editor:*—I found that powdered sulfanilamide healed two infected scalp wounds rapidly. However the powder, serum, blood and pus formed a crust. When this was removed it tore away some of the epithelium. What would be a good base for a sulfanilamide ointment?

E. P. S. Miller, M.D., Chicago.

ANSWER.—The following formula makes a satisfactory sulfanilamide ointment:

1. Dissolve 10 parts of sulfanilamide in 25 parts of hot water (almost boiling). Filter.

2. To 4 parts of sodium alginate add 75 parts of boiling water, emulsify and then strain the resulting mucilaginous mixture through fine gauze. Mix the filtered sulfanilamide solution and the sodium alginate while hot, and stir this mixture until cool.

3. Add 16 parts of anhydrous wool fat, 1 part of sodium chloride dissolved in 4 parts of water, and 78 parts of white petrolatum base to the sulfanilamide-sodium alginate mixture and mix until smooth.

This ointment can be used not only on surface wounds but also on mucous membrane surfaces such as the conjunctivas.

## SULFANILAMIDE ADMINISTRATION TO NURSING MOTHER

*To the Editor:*—What harmful effect if any on a nursing baby 3 weeks old would sulfanilamide have if given to the mother in full doses in a case of puerperal infection?

Thomas E. Brewer, M.D., Quitman, Ark.

ANSWER.—Experience has shown that the amount of sulfanilamide or one of its derivatives which a nursing child might receive from its mother, if she is taking full doses of sulfanilamide or one of its derivatives, would be negligible. So far there have been no reports in medical literature of untoward effects arising in a nursing baby whose mother was receiving sulfanilamide.